Practice guideline update: Acute treatment of migraine in children and adolescents

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society

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N. Licking has no relevant disclosures for this guideline.

M. Sowell has received compensation for serving on a speakers' bureau for Amgen/Novartis Pharmaceuticals; has served as manuscript editor for the journal *Headache* and the *Journal of Child Neurology*, on a speakers' bureau for Allergan, and as an interviewer for *Neurology* podcasts; served as site principal investigator for the CHAMP (Childhood and Adolescent Migraine Prevention) study, for which he received research support from NINDS; and receives research support from Impax Pharmaceuticals.

M. C. Victorio is the site primary investigator for a childhood and adolescent migraine prevention study funded by the National Institutes of Health and site investigator for a pediatric migraine treatment study funded by Impax Laboratories, both studies were contracted through Akron Children's Hospital; has received funding for travel to meetings of the Registry Committee and Quality and Safety Subcommittee by the AAN; has received honoraria for authoring and coauthoring chapters in the *Merck Manual* and for authoring an article in *Pediatric Annals*; performs the following clinical procedures in her practice: onabotulinumtoxinA injection for chronic migraine (2%), peripheral nerve block injections (2%).E. Gersz reports no relevant disclosures.

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M. Yonker has served on a scientific advisory board for AMGEN and for Upsher-Smith Pharmaceuticals; has served as a reviewer for the journals *Cephalalgia*, *Headache*, *Pediatrics*, and the *Journal of the Child Neurology Society*; has received research support as a primary investigator from AstraZeneca, Allergan, Avanir, and NINDS; has received funding for travel from the American Headache Society for serving as a presenter at the Scottsdale Headache Symposium; and serves as a consultant to Impax.

Dr. Kenneth Mack has served as an advisor for AMGEN; receives publishing royalties from UpToDate; performs botulinum toxin injections for headache treatment as 5% of his clinical effort; and serves as a member of the *Neurology*® editorial board.

ABBREVIATIONS

American Academy of Neurology (AAN)

conflict of interest (COI)

confidence interval (CI)

emergency department (ED)

Food and Drug Administration (FDA)

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Guideline Development, Dissemination, and Implementation Subcommittee (GDDI)

nasal spray (NS)

oral disintegrating tablet (ODT)

oral solution (OS)

oral tablet (OT)

nonsteroidal anti-inflammatory drug (NSAID)

randomized controlled trial (RCT)

relative risk (RR)

ABSTRACT

Objective: To provide evidence-based recommendations for the acute symptomatic treatment of children and adolescents with migraine.

Methods: We performed a systematic review of the literature and rated risk of bias of included studies according to the American Academy of Neurology classification of evidence criteria. A multidisciplinary panel developed practice recommendations, integrating findings from the systematic review and following an Institute of Medicine-compliant process to ensure transparency and patient engagement. Recommendations were supported by structured rationales, integrating evidence from the systematic review, related evidence, principles of care, and inferences from evidence.

Results: There is evidence to support the efficacy of the use of ibuprofen, acetaminophen (in children and adolescents), and triptans (mainly in adolescents) for the relief of migraine pain, although confidence in the evidence varies between agents. There is high confidence in the evidence that adolescents receiving oral sumatriptan/naproxen and zolmitriptan nasal spray are more likely to be headache free at 2 hours than those receiving placebo. No acute treatments

were effective for migraine-related nausea or vomiting; some triptans were effective for migraine-related phonophobia and photophobia.

Recommendations: Recommendations for the treatment of acute migraine in children and adolescents focus on the importance of early treatment, choosing the route of administration best suited to the characteristics of the individual migraine attack, and providing counselling on lifestyle factors that can exacerbate migraine, including trigger avoidance and medication overuse.

INTRODUCTION

Migraine is a common and disabling condition in children, with population-based studies showing a prevalence of 9.7% (95% confidence interval [CI], 9.4 to 9.9) in female children and adolescents, and 6.0% (5.8-–6.2) in male children and adolescents.[1] Migraine results in a significant medical and financial burden. In adults and children, the estimated annual cost for migraine-associated emergency department (ED) visits in the United States in 2010 was $700 million.[2] In children and adolescents, it is estimated that 250,000 ED visits each year are related to headache, which accounts for 2.1% of total ED visits.[3]

Diagnosis of primary headache disorders is based on clinical criteria specified in the *International Classification of Headache Disorders*.[4] Management of migraine includes acute and preventive therapies as well as behavioral and lifestyle changes. Acute treatments must be carefully selected and individually tailored to a patient's headache pattern, severity, and disability as well as their expectations, needs, and goals of treatment.

The purpose of this guideline is to systematically assess all randomized controlled trials (RCTs) that evaluated acute migraine treatments in children and adolescents. The goal is to provide patients and providers with a synthesis of available evidence regarding acute self-administered treatments that alleviate headache pain and associated symptoms. The guideline seeks to answer the following clinical question:

In children and adolescents with migraine, do acute self-administered treatments, compared with placebo, reduce headache pain and associated symptoms (nausea, vomiting, photophobia, and phonophobia) and maintain headache freedom?

DESCRIPTION OF ANALYTIC PROCESS

In January 2015, the Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) of the American Academy of Neurology (AAN) convened a multidisciplinary panel consisting of 9 AAN physician members and 3 patient representative members to develop this guideline (see appendix e-1 for the AAN GDDI mission and vision and a listing of the members of the AAN GDDI, and appendix e-2 for the process of panel formation for the guideline and managing conflict of interest.). In September 2017, 3 more AAN GDDI Subcommittee physician members were added to the panel to assist with evidence rating and recommendation drafting. This panel was solely responsible for the final decisions about the design, analysis, and reporting of the guideline.

The study protocol and the guideline manuscript were posted for a 30-day public comment period on the AAN website according to the 2011 process manual,[5] in June 2015 and April 2018 respectively. During this public comment period, members of the public and experts had an opportunity to review the draft protocol and draft guideline manuscript. AAN staff sent invitations to review and comment on the guideline to key stakeholders. All comments during public review were individually addressed by the panel and, where appropriate, led to

modification of the draft guideline or recommendations, or informed the updated systematic review.

This guideline was developed according to the process described in the 2011 AAN guideline development process manual[6] as amended and complies with the Institute of Medicine Standards for Systematic Reviews. The authors included RCTs on the acute treatment of migraine in children (individuals younger than 12 years) and adolescents (individuals aged 12–17 years). The authors considered studies published in English and in other languages. Trials of medications administered intravenously in the ED or in an infusion center setting were not included.

Special populations included sexually active adolescents who were of childbearing age. Excluded were patients with syndromes that may be associated with migraine, including cyclic vomiting, abdominal migraine, benign paroxysmal vertigo, and benign paroxysmal torticollis.

The review included all pharmacologic interventions for the acute treatment of nonrefractory migraine. The comparator group was children and adolescents who received placebo for their migraine.

The outcomes evaluated were reduction of headache pain and associated symptoms at specific time points. For headache pain, the most commonly reported outcomes were headache pain improvement, usually termed “headache pain response” and typically quantified as an

improvement in intensity from moderate-to-severe pain to mild or no pain, and headache pain freedom, usually termed "free of headache pain," at specific time points after intervention (typically from 30 minutes to 2 hours). The most commonly reported associated symptoms were freedom from photophobia, phonophobia, nausea, or vomiting at specific time points after intervention.

This guideline updates a previous guideline published in 2004 on the treatment of migraine in children. The panel performed a literature search of articles published between December 1, 2003, and February 15, 2015, and an updated search of articles published between January 1, 2015, and August 25, 2017 (figure e-1). Appendix e-3 presents the complete and validated search strategy. The search was conducted to find articles on both acute and preventive treatment of migraine in children and adolescents, but the panel determined dividing the one guideline into two separate guidelines would make the scope more manageable. Two authors independently reviewed all abstracts and full-text articles for relevance. Articles were included if (1) at least 90% of study participants were aged 0–18 years, (2) the study included a diagnosis of migraine, (3) the study had at least 20 subjects, and 4) treatment was compared with placebo.

The process for abstract review, inclusion and exclusion of studies, risk of bias assessment and data extraction were followed as specified in the GDDI process manual.[6] The authors found 2,482 abstracts relevant to acute or preventive therapy for pediatric migraine. The authors reviewed 313 full-text articles and identified 10 new studies of acute therapy to be included in the guideline. Of the 10 acute treatment studies included in the 2004 guideline, 6 were included

in the current guideline; the other four studies were excluded because they were either Class IV (three studies) or included fewer than 20 participants (1 study).

A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) process[7] was used to develop conclusions. The confidence in the evidence (high, moderate, low, or, very low) was anchored to the error domain—class of evidence, indirectness of evidence, and precision of effect estimate—with the highest risk of error. This confidence was upgraded or downgraded by a maximum of one level based on several other domains (see GDDI process manual[6] for full description of methods).

Relative risk (RR) and the 95% confidence interval (CI) for the outcomes of interest were calculated. The minimal clinically important difference was an RR of 1.25, in which the children in the treated group had a 25% increased likelihood of having the outcome compared with children in the placebo group. An RR less than 1.10 was determined to be clinically unimportant. If multiple studies that evaluated the same intervention/outcome pair were available, only the studies with the lowest risk of bias were used in formulating the confidence-in-evidence statements.

The panel formulated practice recommendations based on the strength of evidence and other factors, including axiomatic principles of care, the magnitude of anticipated health benefits relative to harms, financial burden, availability of interventions, and patient preferences (appendices e-5 and e-6). The panel assigned levels of obligation (A, B, C, U, R) to the

recommendations, using a modified Delphi process. The panel members' judgments supporting the levels of obligation are indicated in appendix e-7. Considerations for future research and recommendations were also developed, and this guideline will be reassessed over time for currency and potential updates, according to the published AAN Guideline Development, Dissemination, and Implementation process.

ANALYSIS OF EVIDENCE

In children and adolescents with migraine, do acute self-administered treatments reduce headache duration and associated symptoms (especially nausea and vomiting) and maintain headache freedom compared with placebo?

Ibuprofen

One Class II study[8] and one Class III study[9] of ibuprofen were identified. In the Class III RCT[9] children aged 6-12 years with migraine were randomized to treatment of a single attack with 7.5 mg/kg oral solution (OS) ibuprofen or placebo. The proportion of children with a headache pain response at 2 hours was significantly greater in participants treated with ibuprofen compared with placebo, with a RR of 1.40 (95% CI, 1.02 to 2.00). The proportion of participants in whom nausea was eliminated was higher in the ibuprofen group compared with the placebo group (RR 1.56; 95% CI, 1.00 to 2.51), with no difference in vomiting, photophobia, and phonophobia. No adverse events were reported.

In the Class II study,[8] children and adolescents with migraine were randomized to a three-way cross-over study of treatment with 15 mg/kg OS acetaminophen, 10 mg/kg OS ibuprofen, and placebo. The proportion of participants with a headache pain response (reduction in severe or moderate headache by at least 2 grades) at 2 hours was significantly higher in the ibuprofen group compared with the placebo group, with a RR of 1.81 (95% CI, 1.18 to 2.85). The proportion of participants with complete resolution of headache at 2 hours was also significantly higher in the group treated with ibuprofen compared with the placebo group, with a RR of 2.15 (95% CI, 1.28 to 3.71). Adverse events were reported in 8 of 81 participants treated with ibuprofen and 9 of 81 participants treated with placebo, with the most common adverse events in the ibuprofen group being nausea (3 of 81 [3.7%]), vomiting (4 of 81 [4.9%]), and gastric pain (1 of 81 [1.2%]).

Conclusions

There is **insufficient evidence** to determine whether children with migraine receiving 7.5 to 10 mg/kg/dose ibuprofen OS are more or less likely than those receiving placebo to be free of nausea at 2 hours (RR 1.40; 95% CI, 1.00 to 1.96; very low confidence, 1 Class III study, downgraded due to imprecision).

Children and adolescents with migraine receiving 7.5 to 10 mg/kg/dose ibuprofen OS are **possibly more likely** than those receiving placebo to have a headache pain response at two hours (RR 1.54; 95% CI, 1.18 to 2.01; low confidence, 1 Class II and 1 Class III study).

Children and adolescents with migraine receiving 7.5 to 10 mg/kg/dose ibuprofen OS are **probably more likely** than those receiving placebo to be free of headache pain at 2 hours (RR of 2.15; 95% CI 1.28 to 3.71); moderate confidence, 1 Class II study, upgraded due to magnitude of effect).

Acetaminophen

The previously described crossover Class II study[8] was the only study identified. The proportion of participants with a headache pain response at 2 hours was significantly greater with acetaminophen compared with placebo, with an RR of 1.46 (1.02, 2.09). The proportion of participants with complete resolution of headache at 2 hours was higher in the acetaminophen group compared with the placebo but was not statistically significant (RR 1.40; 95% CI, 0.77 to 2.56). Adverse events were reported in 4 of 83 (5%) participants receiving acetaminophen and 9 of 81 (11%) receiving placebo. The most common adverse events in those receiving acetaminophen were nausea (2 of 83 [2.4%]) and vomiting (2 of 83 [2.4%]), which were also reported in the placebo group (3 of 81 [3.7%] experienced nausea, and 6 of 81 [7.4%] experienced vomiting).

Conclusions

There is **insufficient evidence** to determine whether children and adolescents with migraine receiving 15mg/kg/dose acetaminophen OS are more or less likely than those receiving placebo

to be free of headache pain at 2 hours (RR 1.40; 95% CI, 0.77 to 2.56; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

Children and adolescents with migraine receiving 15mg/kg/dose acetaminophen OS are **possibly more likely** than those receiving placebo to have a headache pain response at 2 hours (RR 1.46; 95% CI, 1.02 to 2.09; low confidence, 1 Class II study).

Sumatriptan

There are seven studies of sumatriptan.[10-16] Three evaluated the nasal spray formulation (1 Class I, 2 Class II), two evaluated the oral formulation (1 Class I, 1 Class III), and two evaluated a combination tablet of sumatriptan and naproxen (1 Class I, 1 Class II).

Sumatriptan nasal spray

In a Class I study,[10] adolescents aged 12-17 years with migraine were randomly assigned to placebo, 5 mg of sumatriptan nasal spray (NS), or 20 mg of sumatriptan NS. The proportion of adolescents with a headache pain response (reduction in severity from moderate or severe to mild or no pain) was significantly greater with the group receiving 20 mg of sumatriptan NS compared with placebo at 30 minutes (RR 1.27; 95% CI, 1.01 to 1.60), 1 hour (RR 1.17; 95% CI, 1.00 to 1.37), and 2 hours (RR 1.17; 95% CI, 1.02 to 1.35). The 5-mg dose of sumatriptan NS was not superior to placebo at any time point. A higher proportion of adolescents receiving 20 mg of sumatriptan NS were pain free at 2 hours compared with the placebo group, with a RR of

1.46 (95% CI, 1.15 to 1.86). The proportion of adolescents without photophobia and phonophobia two hours after treatment was higher in the group receiving 20 mg of sumatriptan NS (RR 1.12; 95% CI, 1.01 to 1.24). Resolution of other associated symptoms, including nausea and vomiting, did not differ between treatment groups.

In the Class II RCT,[11] adolescents aged 12-17 years with migraine were randomized to receive 5 mg of sumatriptan NS, 10 mg of sumatriptan NS, 20 mg of sumatriptan NS, or placebo for a single migraine attack. The proportion of adolescents with headache relief (reduction in headache pain from moderate or severe to mild or no pain) at one hour was significantly higher in the groups receiving the 10-mg dose (RR 1.35; 95% CI, 1.05 to 1.74) and the 20-mg dose (RR 1.36; 95% CI, 1.05 to 1.76) but not in the group receiving the 5-mg dose. At two hours, the proportion of adolescents with headache relief was significantly higher in the 5-mg-dose group (RR 1.25; 95% CI, 1.02 to 1.53) and the 20-mg-dose group (RR 1.25; 95% CI, 1.06 to 1.48), but not in the 10-mg-dose group. Photophobia and phonophobia were absent at 2 hours in a significantly higher proportion of adolescents treated with 20 mg of sumatriptan NS than of adolescents treated with placebo. The most common adverse event reported was taste disturbance.

In a Class II double blind placebo-controlled crossover trial of children and adolescents aged 8-17 years with migraine,[13] a single dose of sumatriptan NS (10 mg for subjects who weighed 20-39 kg and 20 mg for subjects who weighed more than 40 kg) or matching placebo was administered for one migraine attack each. The proportion of children with headache relief (from

severe or moderate pain to mild or no pain) at 1 hour was significantly higher in those treated with 10 mg of sumatriptan NS (RR 1.98; 95% CI, 1.21 to 3.05) and 20 mg of sumatriptan NS (RR 1.63; 95% CI, 1.05 to 2.51) compared with those treated with placebo. The proportion of children with headache relief at 2 hours was also significantly higher in the groups receiving 10 mg of sumatriptan NS (RR 1.98; 95% CI, 1.27 to 2.91) and 20 mg of sumatriptan NS (RR 1.96; 95% CI, 1.35 to 2.82) than the group receiving placebo. The proportion of children who were headache free at 2 hours was not significantly higher in the sumatriptan-treated groups compared with the placebo group. Associated migraine symptoms were not assessed. No serious adverse effects were observed. The most common complaint was that the medication tasted bad.

Conclusions

Sumatriptan NS 5 mg

There is **insufficient evidence** to determine whether adolescents with migraine receiving **5 mg of sumatriptan NS** are more or less likely than those receiving placebo to:

- have a headache pain response at 30 minutes (RR 1.03; 95% CI, 0.80 to 1.32; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision).
- have a headache pain response at 2 hours (RR 1.14; 95% CI 1.01 to 1.30; very low confidence, 1 Class I and 1 Class II study, confidence in evidence downgraded due to imprecision)
- have resolution of nausea at 2 hours (RR 1.19; 95% CI, 0.96, 1.48; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision)

- be free of photophobia at 2 hours (RR 1.19; 95% CI, 0.96, 1.48; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision)

Adolescents with migraine receiving **5 mg of sumatriptan NS** are **possibly more likely** than those receiving placebo to be free of phonophobia at 2 hours (RR 1.29; 95% CI 1.07 to 1.56; low confidence, 1 Class II study)

Adolescents with migraine receiving **5 mg of sumatriptan NS** are **probably no more likely** than those receiving placebo to

- have a headache pain response at 1 hour (RR 1.05; 95% CI, 0.91 to 1.21; moderate confidence, 1 Class I and 1 Class II study)
- have relief of photophobia and phonophobia at 2 hours (RR 1.09; 95% CI, 0.98 to 1.21; moderate confidence, 1 Class I study)
- have relief of nausea at 2 hours (RR 1.03; 95% CI, 0.96 to 1.11; moderate confidence, 1 Class I and 1 Class II study)
- have relief of vomiting at 2 hours (RR 1.01; 95% CI, 0.98 to 1.05; moderate confidence,
- 1 Class I and 1 Class II study).

Sumatriptan NS 10 mg

There is insufficient evidence to determine whether children and adolescents with migraine receiving 10 mg of sumatriptan NS are more or less likely than those receiving placebo to have a

headache pain response at 2 hours (RR 1.50; 95% CI, 0.93 to 2.41; very low confidence, 2 Class II studies, confidence in evidence downgraded due to imprecision).

There is **insufficient evidence** to determine whether adolescents with migraine receiving **10 mg of sumatriptan NS** are more or less likely than those receiving placebo to

- have resolution of nausea at 2 hours (RR 1.11; 95% CI, 0.97 to 1.27; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision)
- have resolution of photophobia at 2 hours (RR 1.10; 95% CI, 0.88 to 1.37; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).
- have resolution of phonophobia at 2 hours (RR 1.20; 95% CI, 0.99 to 1.46, very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision

Adolescents with migraine receiving **10 mg of sumatriptan NS** are **possibly no more likely** than those receiving placebo to have resolution of vomiting at 2 hours (RR 1.00; 95% CI, 0.94 to 1.07; low confidence, 1 Class II study)

Children and adolescents with migraine receiving **10 mg of sumatriptan NS** are **possibly more likely** than those receiving placebo to have a headache pain response at 1 hour (RR 1.55; 95% CI, 1.08 to 2.23; low confidence, 2 Class II studies, confidence in evidence downgraded due to imprecision).

Sumatriptan NS 20 mg

There is **insufficient evidence** to determine whether adolescents with migraine receiving **20 mg of sumatriptan NS** are more or less likely than those receiving placebo to

- have relief of photophobia and phonophobia at 2 hours (RR 1.12; 95% CI, 1.01 to 1.24; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision)
- have relief of photophobia at 2 hours (RR 1.24; 95% CI, 1.00 to 1.54, 1 Class II study, confidence in evidence downgraded due to imprecision)

Children and adolescents with migraine receiving **20 mg of sumatriptan NS** are **possibly more likely** than those receiving placebo to

- have a headache pain response at 60 minutes (RR 1.27; 95% CI, 1.09 to 1.49; low confidence, 1 Class I and 2 Class II studies, confidence in evidence downgraded due to imprecision
- have a headache pain response at 2 hours (RR 1.32; 95% CI, 1.04 to 1.68; low confidence, 1 Class I and 2 Class II studies, confidence in evidence downgraded due to imprecision)

Adolescents with migraine receiving **20 mg of sumatriptan NS** are **possibly more likely** than those receiving placebo to

- have a headache pain response at 30 minutes (RR 1.27; 95% CI, 1.01 to 1.60; low confidence, 1 class I study, confidence in evidence downgraded due to imprecision)

- be free of phonophobia at 2 hours (RR 1.34; 95% CI 1.11 to 1.62, 1 Class II study)

Children and adolescents with migraine receiving **20 mg of sumatriptan NS** are **probably more likely** than those receiving placebo to be free of headache pain at 2 hours (RR 1.46; 95% CI, 1.21 to 1.77; moderate confidence, 1 Class I and 2 Class II studies)

Adolescents with migraine receiving **20 mg of sumatriptan NS** are **probably no more likely** than those receiving placebo to

- have relief of nausea at 2 hours (RR 1.02; 95% CI, 0.94 to 1.11; moderate confidence, 1 Class I study)
- have no symptoms of vomiting at 2 hours (RR 1.02, 95% CI, 0.99 to 1.05; moderate confidence, 1 Class I study).

Oral sumatriptan

In a Class I study, [14] children and adolescents aged 10-17 years with migraine were randomly assigned to placebo, 25 mg of sumatriptan oral table (OT), or 50 mg of sumatriptan OT in a single-attack study. The proportion of children adolescents with pain relief (a 2-point reduction in pain on a 5-point scale) was not different among those treated with placebo, 25 mg of sumatriptan, or 50 mg of sumatriptan at 30 minutes, 1 hour, or 2 hours, nor was the proportion of adolescents who were pain free at 2 hours. There was no difference between the groups receiving sumatriptan and the group receiving placebo in the percentage of patients who were free of photophobia, phonophobia, or nausea at 2 hours. The overall incidence of adverse effects was similar between groups, with no serious adverse effects.

A Class III randomized double-blind placebo-controlled crossover study in children and adolescents of sumatriptan OT (50 or 100 mg depending on body surface area) versus placebo[15] also failed to detect a difference between oral sumatriptan and placebo in pain relief at 2 hours.

Conclusions

Sumatriptan 25 mg OT

There is insufficient evidence to determine whether children and adolescents with migraine receiving 25 mg sumatriptan OT are more or less likely than those receiving placebo to

- have a headache pain response at 30 minutes (RR 0.35; 95% CI, 0.03 to 4.14; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision).
- have a headache pain response at 1 hour (RR 0.49; 95% CI, 0.16 to 1.48; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision)
- have a headache pain response at 2 hours (RR 0.86; 95% CI, 0.48 to 1.46; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision)
- be free of headache pain at 2 hours (RR 0.85; 95% CI, 0.42 to 1.46; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision)

Sumatriptan 50 mg OT

There is insufficient evidence to determine whether children and adolescents with migraine receiving 50-mg sumatriptan OT are more or less likely than those receiving placebo to

- have a headache pain response at 30 minutes (RR 2.27; 95% CI, 0.58 to 8.90; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision)
- have a headache pain response at 1 hour (RR 0.39; 95% CI, 0.13 to 1.19; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision).
- have a headache pain response at 2 hours (RR 0.76; 95% CI, 0.44 to 1.32; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision)
- be free of headache pain at 2 hours (RR 0.68; 95% CI, 0.34 to 1.38; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision).

Sumatriptan/naproxen combination OT

In a Class I study of the use of sumatriptan/naproxen OT versus placebo in adolescents aged 12-17 years with migraine,[16] subjects entered a 12-week run-in phase, treating one moderate to severe migraine with single blind placebo. Subjects reporting headache pain 2 hours after dosing were randomly assigned to placebo, sumatriptan/naproxen OT 10/60 mg, sumatriptan/naproxen OT 30/180 mg, or sumatriptan/naproxen OT 85/500 mg. The proportion of adolescents who were pain free at 2 hours was significantly greater with all three doses of sumatriptan/naproxen OT compared with placebo, with an RR of 2.96 (95% CI, 1.65 to 5.26) with sumatriptan/naproxen OT 10/60 mg, an RR of 2.72 (95% CI, 1.51 to 4.88) with sumatriptan/naproxen OT 30/180 mg, and an RR of 2.43 (95% CI, 1.39 to 4.29) with sumatriptan/naproxen OT 85/500 mg. All three doses of sumatriptan/naproxen OT were more effective than placebo for phonophobia at 2 hours, while only the sumatriptan/naproxen OT 10/60 mg and sumatriptan/naproxen OT 85/500 mg were significantly more effective than placebo for photophobia. A greater proportion of

adolescents receiving the sumatriptan/naproxen OT 10/60 mg doses were free of nausea at 2 hours compared with placebo. The most common adverse events were nasopharyngitis, hot flush, and muscle tightness.

In a Class II multi-attack crossover study of sumatriptan/naproxen OT 85/500 mg versus placebo in adolescents aged 12-17 years with migraine,[12] adolescents treated up to four attacks with either sumatriptan/naproxen OT or placebo. A greater proportion of adolescents with migraine treated with sumatriptan/naproxen OT were pain free at 2 hours compared with those treated with placebo, with a RR of 1.98 (95% CI, 1.22 to 3.35). Incidence of adverse events was 10.8% in the sumatriptan/naproxen group and 3% in the placebo group. The most common adverse effects included neck spasm/tension, drowsiness, throat tightness, jaw tightness, dizziness, shoulder tightness, and nausea.

Conclusions

Sumatriptan/naproxen OT 10/60 mg

There is **insufficient evidence** to determine whether adolescents with migraine receiving **sumatriptan/naproxen OT 10/60 mg** are more or less likely than those receiving placebo to be free of nausea at 2 hours (RR 1.17; 95% CI, 1.01 to 1.35; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision).

Adolescents with migraine receiving **sumatriptan/naproxen OT 10/60 mg** are **probably more likely** than those receiving placebo to

- be free of phonophobia at 2 hours (RR 1.45; 95% CI, 1.13 to 1.87; moderate confidence, 1 Class I study)
- be free of photophobia at 2 hours (RR 1.45; 95% CI, 1.12 to 1.87; moderate confidence, 1 Class I study).

Adolescents with migraine receiving **sumatriptan/naproxen OT 10/60 mg** are **more likely** than those receiving placebo to be free of headache pain at 2 hours (RR 2.95; 95% CI, 1.65 to 5.27; high confidence, 1 Class I study, confidence in evidence upgraded due to magnitude of effect).

Sumatriptan/naproxen OT 30/180 mg

There is **insufficient evidence** to determine whether adolescents with migraine receiving **sumatriptan/naproxen OT 30/180 mg** are more or less likely than those receiving placebo to

- be free of photophobia at 2 hours (RR 1.19; 95% CI, 0.90 to 1.58; very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision).
- be free of nausea at 2 hours (RR 1.10; 95% CI, 0.94 to 1.28; very low confidence, 1 Class I study; confidence in evidence downgraded due to imprecision).

Adolescents with migraine receiving **sumatriptan/naproxen OT 30/180 mg** are **possibly more likely** than those receiving placebo to be free of phonophobia at 2 hours (RR 1.38; 95% CI, 1.07

to 1.78; low confidence, 1 Class I study; confidence in evidence downgraded due to imprecision).

Adolescents with migraine receiving **sumatriptan/naproxen OT 30/180 mg** are **more likely** than those receiving placebo to be free of headache pain at 2 hours (RR 2.72; 95% CI, 1.51 to 4.89; high confidence, 1 Class I study, confidence in evidence upgraded due to magnitude of effect).

Sumatriptan/naproxen OT 85/500 mg

Adolescents with migraine receiving **sumatriptan/naproxen OT 85/500 mg** are **probably no more likely** than those receiving placebo to be free of nausea at 2 hours (RR 1.00; 95% CI, 0.86 to 1.16; moderate confidence, 1 Class I study).

Adolescents with migraine receiving **sumatriptan/naproxen OT 85/500 mg** are **probably more likely** than those receiving placebo to

- be photophobia free at 2 hours (RR 1.44; 95% CI, 1.14 to 1.82; moderate confidence, 1 Class I study)
- be phonophobia free at 2 hours (RR 1.43; 95% CI, 1.14 to 1.80; moderate confidence, 1 Class I study).

Adolescents with migraine receiving **sumatriptan/naproxen OT 85/500 mg** are **more likely** than those receiving placebo to be free of headache pain at 2 hours (RR 2.17; 95% CI, 1.49 to 3.16; high confidence, 1 Class I study, I Class II study, confidence in evidence upgraded due to magnitude of effect).

Rizatriptan

Three class II studies of rizatriptan for the treatment of migraine in children and adolescents were identified[17-19]. One Class II study in adolescents evaluated the use of 5 mg of rizatriptan oral disintegrating tablet (ODT) versus placebo for an acute migraine attack with up to two recurrences.[17] There was no difference in the primary efficacy outcome, the proportion of pain free patients at 2 hours, between rizatriptan ODT and placebo (RR 1.14; 95% CI, 0.81 to 1.62) or in the proportion of patients with pain relief (mild or no pain at 2 hours (RR 1.17; 95% CI, 0.97 to 1.41). Associated symptoms of nausea were lower in the rizatriptan group at 1 hour, 1.5 hours, and 4 hours after receiving the dose. However, the baseline percentage of subjects with nausea was higher in the placebo group. There was no difference between rizatriptan and placebo groups in vomiting or photophobia. A significant improvement in phonophobia with rizatriptan, was present at 30 minutes and 4 hours but not at 2 hours. Rizatriptan was well tolerated, with drug-related adverse events in 22.1% versus 23.8% in the placebo group. The most common adverse events were dizziness (4.7%), dry mouth (4.7%), and asthenia (3.4%) in the rizatriptan group and nausea (8.2%) and somnolence (8.2%) in the placebo group.

In a Class II study of adolescents aged 12-17 years with migraine,[18] 476 subjects were randomized to placebo or 5-mg rizatriptan ODT, scheduled to be taken within 30 minutes of onset of a single attack of moderate or severe migraine headache. There was no difference between the rizatriptan group and the placebo group in the proportion of adolescents who had pain relief at 2 hours (RR 0.99; 95% CI, 0.88 to 1.12) or who were pain free at 2 hours (RR 1.25; 95% CI, 0.98 to 1.60). There was no statistically significant difference between treatment groups in any of the associated symptoms at any time point (raw data not given). The most common adverse effects were somnolence, dizziness, dry mouth, and nausea, with no significant differences between treatment groups.

A two-stage Class II study examined the use of 5 mg or 10 mg of rizatriptan ODT (depending on subjects' weight) versus placebo for a single migraine attack,[19] in children and adolescents aged 6-17 years with migraine and an unsatisfactory response to nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. The purpose of stage one was to identify placebo nonresponders. Subjects in this stage were randomized 20:1 to placebo or rizatriptan within 30 minutes of onset of a moderate or severe migraine. Children with mild or no pain after 15 minutes of treatment took no further study medication, whereas patients with moderate to severe pain went on to stage two. Nonresponders who received placebo in stage one were randomized 1:1 to rizatriptan: placebo; nonresponders who received rizatriptan in stage one were allocated to placebo in stage two. A significantly greater proportion of children who received rizatriptan were pain free at two hours compared with those who received placebo, with a RR of 1.36 (95% CI, 1.09 to 1.71). There was no significant difference between the rizatriptan group and the placebo group in the proportion of children with pain relief (from moderate to severe to mild or no pain) at two hours,

or photophobia, phonophobia, and vomiting at two hours. A significantly greater proportion of subjects receiving rizatriptan had no nausea at two hours compared with subjects receiving placebo (RR 1.11; 95% CI, 1.04 to 1.18). There was no difference between the rizatriptan group and the placebo group in the rate of drug-related adverse events. The most common adverse effects with rizatriptan were somnolence, nausea, and fatigue, which occurred with equal frequency in the placebo group.

Conclusions

There is **insufficient evidence** to determine whether children and adolescents with migraine receiving 5 mg or 10 mg of rizatriptan ODT are more or less likely than those receiving placebo to

- be free of nausea at 2 hours (RR 1.11; 95% CI, 1.04 to 1.18; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).
- be free of photophobia at 2 hours (RR 1.11; 95% CI, 0.98 to 1.25; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

Children and adolescents with migraine receiving 5 mg or 10 mg of rizatriptan ODT are **possibly no more likely** than those receiving placebo to be free of vomiting at 2 hours (RR 1.02; 95% CI, 0.99 to 1.05; low confidence, 1 Class II study).

Children and adolescents with migraine receiving 5 mg or 10 mg of rizatriptan ODT are **probably no more likely** than those receiving placebo to

- have a headache pain response at 2 hours (RR 1.07; 95% CI, 0.97 to 1.17; moderate confidence, 3 Class II studies)
- be free of phonophobia at 2 hours (RR 1.07; 95% CI, 0.97 to 1.18; moderate confidence, 2 Class II studies.)

Children and adolescents with migraine receiving 5 mg or 10 mg of rizatriptan ODT are **possibly more likely** than those receiving placebo to be free of headache pain at 2 hours (RR 1.28; 95% CI, 1.10 to 1.48; low confidence, 3 Class II studies, confidence in evidence downgraded due to imprecision).

Almotriptan

In a Class II study of almotriptan for migraine in adolescents,[20] subjects aged 12-17 years were randomized to 6.25 mg of almotriptan OT, 12.5 mg of almotriptan OT, 25 mg of almotriptan OT, or placebo for a single attack. The proportion of adolescents with pain relief (decrease from moderate to severe to mild or no pain) at 2 hours was significantly higher than placebo for the group receiving 6.25 mg of almotriptan (RR 1.30; 95% CI, 1.10 to 1.53), 12.5 mg of almotriptan (RR 1.32; 95% CI, 1.13 to 1.56), and 25 mg almotriptan (RR 1.21; 95% CI, 1.02 to 1.43), although the lower confidence limit of the 25-mg dose fell below the margin for a clinically important effect. There was no difference between placebo and almotriptan at any dose in the proportion of adolescents who were pain free at two hours or in the incidence of nausea, photophobia, or phonophobia at two hours. The proportion of adolescents with one or more adverse effects was 18.6% with placebo, 15.0% with 6.25 mg of almotriptan, 23.6% with 12.5

mg of almotriptan, and 25.8% with 25 mg of almotriptan. The most common adverse effects were dizziness, somnolence, and nausea.

Conclusions

Almotriptan 6.25 mg OT

There is **insufficient evidence** to determine whether adolescents with migraine receiving **6.25 mg of almotriptan** OT are more or less likely than those receiving placebo to be free of headache pain at 2 hours (RR 1.04; 95% CI, 0.78 to 1.39; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

Adolescents with migraine receiving **6.25 mg of almotriptan** OT are **possibly more likely** than those receiving placebo to have a headache pain response at 2 hours (RR 1.30; 95% CI, 1.10 to 1.53; low confidence, 1 Class II study).

Almotriptan 12.5 mg

Adolescents with migraine receiving **12.5 mg of almotriptan** OT are **possibly no more likely** than those receiving placebo to be free of headache pain at 2 hours (RR 1.20; 95% CI, 0.91 to 1.58, low confidence, 1 Class II study).

Adolescents with migraine receiving **12.5 mg of almotriptan** OT are **possibly more likely** than those receiving placebo to have a headache pain response at 2 hours (RR 1.31; 95% CI, 1.11 to 1.54; low confidence, 1 Class II study).

Almotriptan 25 mg OT

There is **insufficient evidence** to determine whether adolescents with migraine receiving **25 mg of almotriptan** OT are more or less likely than those receiving placebo to

- have a headache pain response at 2 hours (RR 1.21; 95% CI, 1.02 to 1.43; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision)
- be free of headache pain at 2 hours (RR 1.18; 95% CI 0.90 to 1.55; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

Zolmitriptan NS

One Class I study[21] and one Class II study[22] of the use of zolmitriptan NS for the treatment of migraine in adolescents were identified. In the Class II study,[22] after a single-blind placebo challenge, non-responders after 15 minutes were randomized to 5 mg of zolmitriptan NS or placebo in a double-blind crossover design. The proportion of adolescents with a headache response (improvement in headache by 2 points on a 4-point scale) at one hour was significantly higher in the group receiving zolmitriptan, with a RR of 1.34 (95% CI, 1.06 to 1.71). A greater proportion of adolescents receiving zolmitriptan were pain free at one hour (RR 2.71; 95% CI, 1.54 to 4.79) and at two hours (RR 2.07; 95% CI, 1.39 to 3.13). A significantly greater proportion of adolescents receiving zolmitriptan was free of photophobia (RR 1.66; 95% CI, 1.03 to 2.68) and phonophobia (RR 1.68; 95% CI, 1.03 to 2.74) at 30 minutes. The most common adverse events in adolescents receiving zolmitriptan were taste disturbance (6.5%), nasal discomfort (2.5%), nasal congestion (1.5%) and dizziness (1.5%).

The Class I study[21] evaluated the use of zolmitriptan NS versus placebo to treat a single migraine attack. Participants completed a 30-day run-in period, during which a single migraine attack was treated with single-blind placebo NS. Participants who did not respond to placebo were randomized to one of three zolmitriptan NS doses (5 mg, 2.5 mg, or 0.5 mg) or placebo for a subsequent migraine attack. A planned interim futility analysis determined that the 0.5 mg and 2.5 mg doses were futile, relative to placebo, and further randomization to these treatment arms was discontinued. Only the 5-mg dose was evaluated for efficacy. The proportion of adolescents who were pain free at two hours was significantly higher with zolmitriptan NS compared with placebo (RR, 1.79; 95% CI, 1.28 to 2.51), as was the proportion of adolescents with a headache response at two hours (RR, 1.29; 95% CI, 1.06 to 1.58). There was no statistically significant reduction in the occurrence of nausea or vomiting in the group receiving zolmitriptan compared with the group receiving placebo (data were not provided in the manuscript). The proportion of adolescents without photophobia and without phonophobia at two hours was higher in the group receiving zolmitriptan than in the group receiving placebo (RR, 1.26 [95% CI, 1.05 to 1.51] and 1.21 [95% CI, 1.02 to 1.44], respectively). No serious adverse effects or adverse effects leading to discontinuation were reported. Dysgeusia was the most frequently reported adverse effect. No clinically meaningful differences were observed in vital signs, hematology, clinical chemistry, urinalysis, or electrocardiogram parameters.

Conclusions

There is **insufficient evidence** to determine whether adolescents with migraine receiving zolmitriptan NS 5 mg are more or less likely than those receiving placebo to be free of phonophobia at two hours (RR 1.21; 95% CI, 1.02 to 1.44, very low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision).

Adolescents with migraine receiving zolmitriptan NS 5 mg are **possibly more likely** than those receiving placebo to

- have a headache pain response at one hour (RR 1.34; 95% CI, 1.05 to 1.71; low confidence, 1 Class II study).
- have a headache pain response at two hours (RR 1.29; 95% CI, 1.06 to 1.58; low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision)
- have a sustained headache pain response at two hours (RR 1.55; 95% CI, 1.16 to 2.08; low confidence, 1 Class II study).
- be free of photophobia at two hours (RR 1.26; 95% CI, 1.05 to 1.51, low confidence, 1 Class I study, confidence in evidence downgraded due to imprecision).

Adolescents with migraine receiving zolmitriptan NS 5 mg are **probably more likely** than those receiving placebo to

- be free of headache pain at one hour (RR 2.71; 95% CI, 1.54 to 4.78; moderate confidence, 1 Class II study, confidence in evidence upgraded due to magnitude of effect).

- be free of photophobia at 30 minutes (RR 1.66; 95% CI, 1.03 to 2.68, moderate confidence, 1 Class II study, confidence in evidence upgraded due to magnitude of effect).
- be free of phonophobia at 30 minutes (RR 1.68; 95% CI, 1.03 to 2.74, moderate confidence, 1 Class II study, confidence in evidence upgraded due to magnitude of effect).

Adolescents with migraine receiving zolmitriptan NS 5 mg are **more likely** than those receiving placebo to be free of headache pain at two hours (RR 1.90; 95% CI, 1.47 to 2.46; high confidence, 1 Class I study and 1 Class II study, confidence in evidence upgraded due to magnitude of effect).

Eletriptan

A single Class II study of the use of eletriptan for adolescents with migraine was identified.[23] Subjects were randomized to 40 mg eletriptan OT or placebo for an acute migraine attack. There was no difference between eletriptan and placebo in the proportion of adolescents with a headache response at 2 hours, a pain free response at 2 hours, or nausea, photophobia or phonophobia at 2 hours. Eletriptan was well tolerated, with more adverse events than placebo (42.6% versus 28.3%). The most common adverse events for subjects receiving eletriptan were somnolence (8.5%), dizziness (7.8%), asthenia (5.4%), and nausea (3.9%).

Conclusions

There is **insufficient evidence** to determine whether adolescents with migraine receiving eletriptan OT 40 mg are more or less likely than those receiving placebo to be free of headache pain at 2 hours (RR 1.46; 95% CI, 0.88 to 2.42; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

Adolescents with migraine receiving eletriptan OT 40 mg are **possibly no more likely** than those receiving placebo to

- have a headache pain response at 2 hours (RR 0.99; 95% CI, 0.81 to 1.21; low confidence, 1 Class II study)
- be free of nausea at 2 hours (RR 0.96; 95% CI, 0.84 to 1.10, low confidence, 1 Class II study)
- be free of photophobia at 2 hours (RR 0.97; 95% CI, 0.85 to 1.10, low confidence, 1 Class II study).
- be free of phonophobia at 2 hours (RR 1.05; 95% CI, 0.89 to 1.24, low confidence, 1 Class II study).

PRACTICE RECOMMENDATIONS

A. Establish a specific headache diagnosis

Rationale

The appropriate care of a patient with headaches requires establishing a correct diagnosis [PRIN]. This affects our diagnostic approach, treatment, and prognosis. Headaches may be classified as primary (migraine, tension-type, trigeminal autonomic cephalalgia), secondary (related to another condition [e.g., infection, trauma, tumor]), or other headache syndromes (painful cranial neuropathies, facial pain, and other headache) [PRIN].[4] Patients with signs and symptoms of secondary headache, such as sudden change in headache, papilledema, focal deficits, and the additional presence of seizures, require further evaluation beyond a thorough history and physical examination. When migraine is diagnosed, tailored treatments may be considered that can result in improved outcomes and quality of life [RELA].[24] Diagnostic criteria for pediatric migraine include at least five headaches over the past year that last 2-72 hours when untreated, with two of four additional features (pulsatile quality, unilateral or, worsening with activity or limiting activity, moderate to severe in intensity), and association with at least nausea or vomiting, or photophobia and phonophobia. These associated symptoms can be inferred by family report of the child's activities. The time a child sleeps can be considered part of the headache duration. Auras typically occur in about one third of older children and adolescents and precede the headache by 5-60 minutes [PRIN].[4]

Recommendations

1a. When evaluating children and adolescents with headache, clinicians should diagnose a specific headache type (primary, secondary, or other headache syndrome) (Level B).

1b. When evaluating children and adolescents with headache, clinicians should ask about premonitory and aura symptoms, headache semiology (onset, location, quality, severity, frequency, duration, aggravating and alleviating factors), associated symptoms (nausea, vomiting, phonophobia and photophobia), and pain-related disability in order to improve diagnostic accuracy for migraine and appropriately counsel the patient (Level B).

B Acute migraine treatment (see Table 1, Pain Outcomes and Confidence in Evidence)

Rationale Migraine treatment should aim to achieve fast, complete pain relief, with minimum side effects [PRIN]. Associated symptoms like nausea, vomiting, photophobia, and phonophobia should also be addressed. In adults, early treatment of migraine (within less than one hour of headache onset) improves pain-free rates [RELA].[25] Improved efficacy with early treatment is likely to be seen in children and adolescents as well [INFER]. Many children and adolescents use and benefit from nonprescription oral analgesics like acetaminophen, ibuprofen, and naproxen [RELA].[26] Triptans are less commonly prescribed in children than in adults, and only almotriptan OT (for patients aged 12 years and older), rizatriptan ODT (for patients aged 6-17 years), sumatriptan/naproxen OT (for patients aged 12 years and older), and zolmitriptan NS (for patients aged 12 years and older) are approved by the Food and Drug Administration (FDA) for use in children. Ergots and oral naproxen alone have not been studied in children.

Recommendations

2a. Clinicians should counsel that acute migraine treatments are more likely to be effective when used earlier in the migraine attack, when pain is still mild (Level B).

2b. Clinicians should prescribe ibuprofen OS (10 mg/kg) as an initial treatment option to reduce pain in children and adolescents with migraine (Level B).

2c. For adolescents with migraine, clinicians should prescribe sumatriptan/naproxen OT (10/60 mg, 30/180 mg, 85/500 mg), zolmitriptan NS (5 mg), sumatriptan NS (20 mg), rizatriptan ODT (5 mg or 10 mg), or almotriptan OT (6.25 mg or 12.5 mg) to reduce headache pain (Level B).

Rationale

Patients respond differently to the same medication [PRIN]. In adults, failure to respond to one triptan does not preclude response to an alternate triptan [RELA].[27] In adults who respond to a triptan but have recurrence of their headache within 24 hours, taking a second dose is effective [RELA].[28] Children might have the same experience [INFER], but product monograph daily maximum doses must be followed [PRIN]. Migraine features (severity, associated symptoms, disability, and most bothersome symptoms) differ among individuals and among different attacks in the same individual [RELA].[29] Intranasal sumatriptan and zolmitriptan are absorbed more quickly than the oral form [RELA][30, 31] and has a faster onset of action [RELA].[32, 33] For migraines that rapidly peak in severity or are associated with nausea and vomiting, non-oral forms of treatment may be more effective [INFER]. Thus, children with migraine may benefit from more than one acute treatment choice and different delivery routes, depending on their individual headache characteristics [INFER].

Recommendations

3a. Clinicians should counsel patients and families that a series of medications may need to be used to find treatments that most benefit the patient (Level B).

3b. Clinicians should instruct patients and families to use the medication that best treats the characteristics of each migraine to provide the best balance of efficacy, side effects, and patient preference (Level B).

3c. Clinicians should offer an alternate triptan if one triptan fails to provide pain relief to find the most effective agent to reduce migraine symptoms (Level B).

3d. Clinicians may prescribe a non-oral route when headache peaks in severity quickly, is accompanied by nausea and/or vomiting, or oral formulations fail to provide pain relief (Level C).

3e. Clinicians should counsel patients and families that if their headache is successfully treated by their acute migraine medication but headache recurs within 24 hours of their initial treatment, taking a second dose of acute migraine medication can treat the recurrent headache (Level B).

Rationale

Sumatriptan/naproxen OT (10/60 mg, 30/180 mg, and 85/500 mg tablet) is more likely than placebo to result in headache pain-free status at 2 hours [EVID]. Sumatriptan and naproxen have a different pharmacokinetic profiles targeted to aid in migraine relief [RELA].[34] In adults, the sumatriptan/naproxen combination OT is more effective than monotherapy with either component [RELA].[35] Because of cost and insurance issues, not all patients have access to all

available formulations of medications [PRIN]. Given the distinct mechanisms of action among medications in the triptan class and the NSAID class [PRIN], the addition of an NSAID to a triptan may improve rates of pain response and pain-free status [INFER].

Recommendation

4. In adolescents whose migraine is incompletely responsive to a triptan, clinicians should offer ibuprofen or naproxen in addition to a triptan to improve migraine relief (Level B).

C. Treatment of associated symptoms (see Table 2, Associated Symptoms Outcomes and Confidence in Evidence)

Rationale

Migraine is typically accompanied by other symptoms (nausea, vomiting, photophobia, phonophobia) in addition to head pain [PRIN]. Anti-emetics are often prescribed along with specific (triptan) and nonspecific (NSAID) migraine treatments to address nausea and vomiting and to speed the rate of medication absorption [PRIN]. In pediatric migraine trials, the treatment effects on migraine-associated symptoms were less pronounced than the treatment effects on pain [EVID]. While photophobia and phonophobia were responsive to zolmitriptan nasal spray and sumatriptan/naproxen [EVID], none of the treatments studied had demonstrated effectiveness against nausea or vomiting [EVID]. Antiemetics are available to treat nausea and vomiting related to other pediatric conditions (acute gastroenteritis, postoperative state,

chemotherapy) [RELA][36, 37] and may be of benefit for migraine-associated nausea, although no clinical trials specifically evaluating anti-emetics for pediatric migraine-associated nausea have been performed [INFER]. Nasal spray formulations of zolmitriptan and sumatriptan may be easier to administer in adolescents with migraine with prominent nausea and/or vomiting [PRIN].

Recommendations

5. For children and adolescents with migraine who experience prominent nausea and/or vomiting, clinicians should offer additional anti-emetic treatments (Level B).

D. Counseling recommendations

Rationale

Patient education can improve patient safety and adherence to interventions [PRIN]. It is important to learn about the behavioral aspects of self-care that might improve migraine, including healthy habits with lifestyle modification, potential migraine triggers/aggravating factors, and the risk of overusing medication [INFER]. Maintaining a headache diary is helpful to track response to any new therapy. Patients and families will benefit from understanding the limitations of current available treatments [INFER]. Overuse of medication to treat acute attacks has been associated with medication overuse headache in adults [RELA][38] but has not been well-

studied in children. Methods to prevent medication overuse headache are included in adult treatment plans [PRIN].

Recommendations

6a. Clinicians should counsel children and adolescents with migraine and their families about migraine-healthy habits, including lifestyle modification, and identification/disproving/resolution of migraine triggers/aggravating factors and avoidance of medication overuse (Level B).

6b. Clinicians should make collaborative agreements with children and adolescents with migraine and their families on treatment goals that are individualized to the patient (Level B).

6c. Clinicians may counsel children and adolescents with migraine and their families to maintain a headache diary to monitor their response to treatments (Level C).

6d. Clinicians should counsel patients and families to use no more than 14 days of ibuprofen or acetaminophen per month, no more than 9 days of triptans per month, and no more than 9 days per month of any combination of triptans, analgesics or opioids** for more than three months to avoid medication overuse headache (Level B).

**There is no evidence to support the use of opioids in children with migraine – opioids are included in this statement to be consistent with the International Classification of Headache Society Disorders 3rd edition regarding medication overuse.

E. Contraindications and precautions to triptan use

Rationale

According to the FDA, triptans are contraindicated in patients with a history of cardiovascular disease, including stroke, transient ischemic attacks, myocardial infarction, severe peripheral vascular disease, ischemic bowel disease, and coronary vasospasm, including Prinzmetal angina. Triptans are also contraindicated in patients with cardiac accessory conduction pathway disorders, including Wolff-Parkinson-White syndrome [PRIN]. Although the 2004 American Headache Society consensus statement does not consider these as absolute contraindications,[39] these contraindications (INFER) are based on the known pharmacology of the triptans[40] and triptan effects on vascular muscle [RELA].[41] While these medical contraindications are less prevalent in the pediatric population, they are important to consider.

Recommendation

7. Clinicians must not prescribe triptans to those with a history of ischemic vascular disease or accessory conduction pathway disorders to avoid the morbidity and mortality associated with aggravating these conditions (Level A).

Rationale

In adults who have migraine with typical aura, there is evidence that it is safe to take triptans during the aura, although the triptan may be more effective if taken at the onset of pain [RELA].[42, 43] The use of triptans during the aura phase is of concern because of potential difficulties differentiating early stroke symptoms from migraine aura [PRIN]. While this is

unlikely a problem in those with established migraine with visual aura, caution is warranted in those with more complex aura presentations [PRIN]. According to the FDA, triptans are contraindicated in those with a history of hemiplegic aura or migraine with brainstem aura [PRIN]. This contraindication was based on a view of migraine pathophysiology that is no longer considered current.

Recommendation

8a. Clinicians should counsel adolescent patients with migraine with aura that taking their triptan during a typical aura is safe, but that the triptan may be more effective if taken at the onset of head pain (Level B).

8b. Clinicians may consider referral of children and adolescents with hemiplegic migraine or migraine with brainstem aura who do not respond to other treatments to a headache specialist to find effective treatment (Level C).

SUGGESTIONS FOR FUTURE RESEARCH

Most adults with migraine have onset in childhood or adolescence. Accurate diagnosis and treatment in childhood and adolescence can prevent migraine-related disability and significantly improve quality of life.[24] Lifestyle modifications and acute pharmacologic treatments are the mainstay of migraine management in adults as well as adolescents and children. Although the pathophysiology of migraine in children and adolescents is presumed to be the same as in adults, a higher placebo response is observed in children and adolescents, with a lower therapeutic gain

measured in clinical trials.[44] Patterns of migraine presentation and associated symptoms in children and adolescents evolve into the adult patterns and their shortest headaches may be shorter in duration.[4] This should be considered when designing clinical trials. Additionally, the higher level of response to placebo needs to be addressed when designing trials. Unique trial designs have had some limited success and should be considered further.[45] The fact that all acute treatment trials in children and adolescents are performed after proven efficacy in adults may be a significant contributor to the expectation response and thus contribute to the placebo effect. This expectation response is widely seen in pain studies and may explain why so few trials of acute migraine therapy in children and adolescents have shown positive results.

Although there is a growing body of evidence to support recommendations for the acute treatment of pediatric migraine, challenges remain. Many children and adolescents do not respond to treatment at home with NSAIDs and triptans and seek pain relief at an ED or infusion center.[46] Trials of refractory headache treatment in children and adolescents have been conducted,[47] but therapeutic approaches in these circumstances vary.[48] Studies are also needed of alternate delivery routes for acute treatments such as transdermal patches because oral medications are poorly absorbed in children and adolescents with nausea and vomiting. Regardless of the strategy chosen for acute migraine therapy, treatment plans should be individually tailored to the patient and family and include education about migraine prevention strategies.

DISCLAIMER

Practice guidelines, practice advisories, comprehensive systematic reviews, focused systematic reviews and other guidance published by the American Academy of Neurology and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information: 1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; 2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); 3) addresses only the question(s) specifically identified; 4) does not mandate any particular course of medical care; and 5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. AAN provides this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

CONFLICT OF INTEREST

The AAN is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2011 AAN process manual, as amended.[5].

Table 1 Pain Outcomes and Confidence in Evidence

Outcome	High confidence (more likely than placebo)	Moderate confidence (probably more likely than placebo)	Low confidence (possibly more likely than placebo)	Moderate confidence (probably no more likely than placebo)	Low confidence (possibly no more likely than placebo)	Very low confidence (insufficient evidence)
Pain response at 30 minutes			sumatriptan NS 20 mg			sumatriptan NS 5 mg sumatriptan OT 25 mg sumatriptan OT 50 mg
Pain response at 1 hour			zolmitriptan NS 5 mg sumatriptan NS 10 mg sumatriptan NS 20 mg	sumatriptan NS 5 mg		sumatriptan OT 25 mg sumatriptan OT 50 mg
Pain response at 2 hours			ibuprofen OS 7.5 to 10 mg/kg acetaminophen OS 15mg/kg almotriptan OT 6.25 mg almotriptan OT 12.5 mg sumatriptan NS 20 mg zolmitriptan NS 5 mg	rizatriptan ODT 5 or 10 mg	eletriptan OT 40 mg	almotriptan OT 25 mg sumatriptan NS 5 mg sumatriptan NS 10 mg sumatriptan OT 25 mg sumatriptan OT 50 mg
Pain free at 1 hour		zolmitriptan NS 5 mg				
Pain free at 2 hours	sumatriptan naproxen OT 10/60 mg sumatriptan/naproxen OT 30/180 mg sumatriptan/naproxen OT 85/500 mg zolmitriptan NS 5 mg	ibuprofen OS 7.5 to 10 mg/kg sumatriptan NS 20 mg	rizatriptan ODT 5 or 10 mg		almotriptan OT 12.5 mg	acetaminophen OS 15 mg/kg almotriptan OT 6.25 mg almotriptan OT 25 mg eletriptan OT 40 mg sumatriptan OT 25 mg sumatriptan OT 50 mg

Abbreviations: NS=nasal spray; ODT=oral disintegrating tablet; OS=oral solution; OT=oral tablet

Table 2 Associated Symptom Outcomes and Confidence in Evidence

Outcome	High confidence (more likely than placebo)	Moderate confidence (probably more likely than placebo)	Low confidence (possibly more likely than placebo)	Moderate confidence (probably no more likely than placebo)	Low confidence (possibly no more likely than placebo)	Very low confidence (insufficient evidence)
Relief of nausea at 2 hours				sumatriptan NS 5 mg sumatriptan NS 20 mg sumatriptan/naproxen OT 85/500 mg	eletriptan OT 40 mg	ibuprofen OS 7.5 to 10 mg/kg sumatriptan NS 10 mg sumatriptan/naproxen OT 10/60 mg sumatriptan/naproxen OT 30/180 mg rizatriptan ODT 5 or 10 mg
Relief of vomiting at 2 hours				sumatriptan NS 5 mg sumatriptan NS 20 mg	sumatriptan NS 10 mg rizatriptan ODT 5 or 10 mg	
Relief of photophobia at 30 minutes		zolmitriptan NS 5 mg				
Relief of photophobia at 2 hours		sumatriptan/naproxen OT 10/60 mg sumatriptan/naproxen OT 85/500 mg	zolmitriptan NS 5 mg		eletriptan OT 40 mg	sumatriptan NS 10 mg sumatriptan/naproxen OT 30/180 mg rizatriptan ODT 5 or 10 mg
Relief of phonophobia at 30 minutes		zolmitriptan NS 5 mg				

Relief of phonophobia at 2 hours		sumatriptan/naproxen OT 10/60 mg sumatriptan/naproxen OT 85/500 mg	sumatriptan NS 5 mg sumatriptan NS 20 mg sumatriptan/naproxen OT 30/180 mg	rizatriptan ODT 5 or 10 mg	eletriptan OT 40 mg	sumatriptan NS 10 mg zolmitriptan NS 5 mg

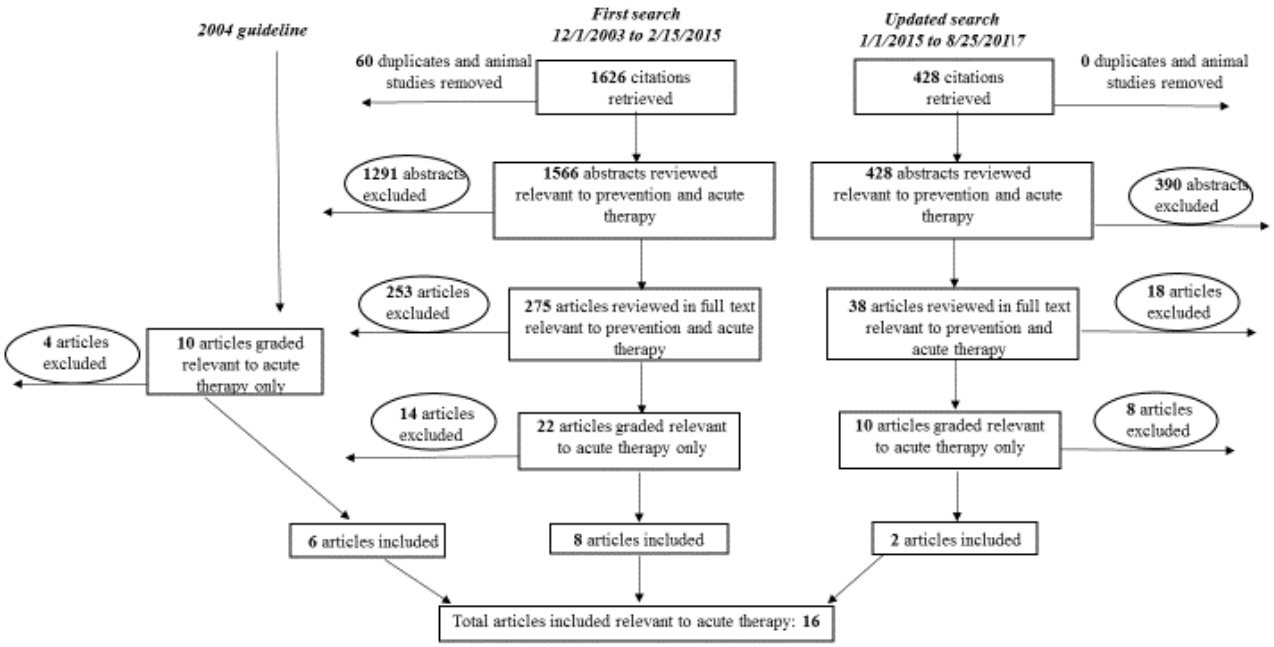
Abbreviations: NS=nasal spray; ODT=oral disintegrating tablet; OS=oral solution; OT=oral tablet

Table 3 Confidence in Evidence by Drug and Outcome

	Pain response at 30 minutes	Pain response at 1 hour	Pain response at 2 hours	Pain free at 1 hour	Pain free at 2 hours	Relief of nausea at 2 hours	Relief of vomiting at 2 hours	Relief of photo-phobia at 2 hours	Relief of phono-phobia at 2 hours
Ibuprofen OS 7.5 to 10 mg/kg			low		moderate	very low			
Acetaminophen OS 15 mg/kg			low		very low				
Sumatriptan OT 25 mg	very low	very low	very low		very low				
Sumatriptan OT 50 mg	very low	very low	very low		very low				
Sumatriptan NS 5 mg	very low	moderate–probably no more likely than placebo	very low			moderate–probably no more likely than placebo	moderate–probably no more likely than placebo		
Sumatriptan NS 10 mg		low	very low			very low	low-possibly no more likely than placebo	very low	very low
Sumatriptan NS 20 mg	low	low	low		moderate	moderate–probably no more likely than placebo	moderate–probably no more likely than placebo		
Sumatriptan/ naproxen OT 10/60 mg					high	very low		moderate	moderate
Sumatriptan/ naproxen OT 30/180 mg					high	very low		very low	Low
Sumatriptan/ naproxen OT 85/500 mg					high	moderate–probably no more likely than placebo		moderate	moderate
Rizatriptan ODT 5 or 10 mg			moderate–probably no more likely than placebo		low	very low	low-possibly no more likely than placebo	very low	moderate–probably no more likely than placebo
Eletriptan OT 40 mg			low-possibly no more likely than placebo		very low	low-possibly no more likely than placebo		low-possibly no more likely than placebo	low-possibly no more likely than placebo
Zolmitriptan NS		low	low	moderate	high			low	very low
Almotriptan OT 6.25 mg			low		very low				
Almotriptan OT 12.5 mg			low		low-possibly no more likely than placebo				
Almotriptan OT 25 mg			very low		very low				

Abbreviations: NS=nasal spray; ODT= oral disintegrating tablet; OS=oral solution; OT=oral tablet

Figure e-1.


2004 guideline
First search
12/1/2003 to 2/15/2015
Updated search
1/1/2015 to 8/25/2017
60 duplicates and animal studies removed
1626 citations retrieved
428 citations retrieved
0 duplicates and animal studies removed
1291 abstracts excluded
1566 abstracts reviewed relevant to prevention and acute therapy
428 abstracts reviewed relevant to prevention and acute therapy
390 abstracts excluded
253 articles excluded
275 articles reviewed in full text relevant to prevention and acute therapy
38 articles reviewed in full text relevant to prevention and acute therapy
18 articles excluded
4 articles excluded
10 articles graded relevant to acute therapy only
14 articles excluded
22 articles graded relevant to acute therapy only
10 articles graded relevant to acute therapy only
8 articles excluded
6 articles included
8 articles included
2 articles included
Total articles included relevant to acute therapy: 16

Appendices

Appendix e-1.

AAN GDDI mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

AAN GDDI members 2017–2019

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD (Co-Vice-Chair); Stephen Ashwal, MD; Lori L. Billinghurst, MD, MSc; Brian Callaghan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Jeffrey Fletcher, MD; David Gloss, MD; Gary S. Gronseth, MD (Senior Evidence-based Medicine Methodology Expert); Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Koto Ishida, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; Mia T. Minen, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Alison Pack, MD;

Tamara Pringsheim, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Navdeep Sangha, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Jacqueline French, MD (Ex-Officio, Guideline Process Historian)

Appendix e-2 Process of Guideline Panel Formation and Management of Conflict of Interest

In January 2015, the Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) of the AAN convened a multidisciplinary panel consisting of nine AAN physician members and three patient representative members to develop this guideline (see appendix e-1 for the AAN GDDI mission and vision and a listing of the members of the AAN GDDI, and appendix e-2 for the process of panel formation for the guideline and managing conflict of interest.). In September 2017, 3 more AAN GDDI Subcommittee physician members were added to the panel (L.B., T.P., and S.P.) to assist with evidence rating and recommendation drafting. The physicians included content experts (A.H., K.M., M.S., C.V., M.Y.), methodology experts (D.G., T.P.), and GDDI Subcommittee members (Y.H.-M., M.O., N.L., S.P., L.B). The patient representatives (E.G., E.L., H.Z) included 2 adolescents and 1 adult who had experienced migraine in childhood. The physicians and patient representatives were required to submit an online conflict of interest (COI) form and a copy of their curriculum vitae. Five of the 15 authors were determined to have COIs which were judged to be not significant enough to preclude them from authorship (A.H., K.M., M.S., C.V., M.Y.). All authors determined to have COIs were not permitted to review or rate the evidence. These individuals were used in an advisory capacity to help with the validation of the key questions, help with the scope of the literature search, help with the identification of seminal articles to validate the literature search, and participate in the recommendation development process. This panel was solely responsible for the final decisions about the design, analysis, and reporting of the guideline.

Appendix e-3: Search strategy

Dates searched: First search: 12/1/2003 to 2/15/2015; Update search: 1/1/2015 to 8/25/2017

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1946 to Present

#	Searches	Results	Search Type
1	exp *headache disorders/dh, dt, pc, th or exp *migraine disorders/dh, dt, pc, th	8610	Advanced
2	(headache* or migraine*).ti.	31395	Advanced
3	(ibuprofen or acetominophen or naproxen).mp.	14976	Advanced
4	(nsaids or "non steroidal antiflammatory*").mp. or exp anti-inflammatory agents, non-steroidal/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	163030	Advanced
5	(triptans or sumatriptan* or rizatriptan or zolmitriptan or naratriptan or almotriptan or frovatriptan or elitritan).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	4189	Advanced
6	exp Serotonin Receptor Agonists/	80602	Advanced

7	(chlorpromazine or dihydroergotamine or ketoralac or diclofenac).mp.	30076	Advanced
8	(acute or prevent* or abort* or prophyla* or nonpharmacolog* or "non-pharmacologic*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2080317	Advanced
9	cyproheptadine.mp. or exp adrenergic beta antagonists/ or "beta block*".mp. or propranolol.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	100243	Advanced
10	exp calcium channel blockers/ or "calcium channel block*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	76878	Advanced
11	flunarizine.mp. or Flunarizine/	1676	Advanced
12	exp adrenergic alpha agonists/ or clonidine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	150524	Advanced
13	exp antidepressive agents, tricyclic/ or antidepressant*.mp. or amitriptyline.mp. [mp=title, abstract, original title, name of substance	66701	Advanced

	word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]		
14	exp serotonin uptake inhibitors/ or venlafaxine.mp. or antihistamine*.mp. or exp histamine h1 antagonists/ or trazodone.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	69292	Advanced
15	exp anticonvulsants/ or anticonvulsant*.mp. or divalproex.mp. or topiramate.mp. or levetiracetam.mp. or zonisamide.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	126907	Advanced
16	(botox or botulinum toxin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	14744	Advanced
17	exp complementary therapies/ or exp vitamins/ or exp dietary supplements/ or petasites.mp. or butterbur.mp. or riboflavin.mp. or ergocalciferol.mp. or magnesium.mp. or exp minerals/ [mp=title, abstract, original title, name of substance word, subject heading word,	673406	Advanced

	keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]		
18	melatonin.mp. or Melatonin/	19716	Advanced
19	biofeedback.mp. or biofeedback, psychology/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	8249	Advanced
20	electric stimulation therapy/ or transcranial magnetic stimulation/ or transcutaneous electric nerve stimulation/ or behavior therapy/ or cognitive therapy/ or mindfulness.mp. or internet.mp. or acupuncture therapy/ or acupuncture analgesia/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	145796	Advanced
21	music therapy.mp. or Music Therapy/	2768	Advanced
22	("cognitive behavior therapy" or cefaly).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1378	Advanced
23	(pizotifen or pizotyline).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,	394	Advanced

	protocol supplementary concept word, rare disease supplementary concept word, unique identifier]		
24	(flunarazine or petadolex or phytotherap* or paracetamol or acetominophen).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	39566	Advanced
25	or/3-7	266591	Advanced
26	or/9-18	1205038	Advanced
27	or/19-24	195195	Advanced
28	(1 or 2) and 8	6834	Advanced
29	(1 or 2) and 25	5077	Advanced
30	(1 or 2) and 26	5330	Advanced
31	(1 or 2) and 27	1776	Advanced
32	28 or 29 or 30 or 31	12496	Advanced
33	limit 32 to (english language and yr="2003 - 2015")	5776	Advanced
34	limit 33 to "all child (0 to 18 years)"	1172	Advanced
35	33 and (preschool* or child* or pediatr* or paediatr* or preteen* or school* or teen* or adolescen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,	1312	Advanced

	protocol supplementary concept word, rare disease supplementary concept word, unique identifier]		
36	34 or 35	1320	Advanced
37	limit 36 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial or "review" or systematic reviews)	732	Advanced
38	36 and (cohort* or prospective* or retrospective* or "comparative effectiveness" or outcome* or "odds ratio" or reproducib* or "confidence interval" or "cross-over" or "sensitivity and specificity" or placebo).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	807	Advanced
39	("case control*" or "meta analysis" or trial*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1479765	Advanced
40	36 and 39	590	Advanced
41	37 or 38 or 40	1036	Advanced

42	41 not (letter or comment or editorial).pt.	1025	Advanced
43	remove duplicates from 42	1021	

Same strategy EBM Reviews – 70

Embase 1988 to 2015 Week 08

#	Searches	Results	Search Type
1	exp "headache and facial pain"/dm, dt, pc, rt, th [Disease Management, Drug Therapy, Prevention, Radiotherapy, Therapy]	29641	Advanced
2	exp migraine/dm, dt, pc, rt, th [Disease Management, Drug Therapy, Prevention, Radiotherapy, Therapy]	14965	Advanced
3	(headache* or migraine*).ti.	34872	Advanced
4	(ibuprofen or acetominophen or naproxen).mp.	44927	Advanced
5	(nsaids or "non steroidal antiflammatory*").mp. or exp anti-inflammatory agents, non-steroidal/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	381700	Advanced
6	(triptans or sumatriptan* or rizatriptan or zolmitriptan or naratriptan or almotriptan or frovatriptan or elitritan).mp. [mp=title, abstract, subject	10273	Advanced

	headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]		
7	exp Serotonin Receptor Agonists/	97903	Advanced
8	(chlorpromazine or dihydroergotamine or ketoralac or diclofenac).mp.	52627	Advanced
9	(acute or prevent* or abort* or prophyla* or nonpharmacolog* or "non-pharmacologic*").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2322312	Advanced
10	cyproheptadine.mp. or exp adrenergic beta antagonists/ or "beta block*".mp. or propranolol.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	188224	Advanced
11	exp calcium channel blockers/ or "calcium channel block*".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	162515	Advanced
12	flunarizine.mp. or Flunarizine/	3792	Advanced
13	exp adrenergic alpha agonists/ or clonidine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	130515	Advanced

14	exp antidepressive agents, tricyclic/ or antidepressant*.mp. or amitriptyline.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	138777	Advanced
15	exp serotonin uptake inhibitors/ or venlafaxine.mp. or antihistamine*.mp. or exp histamine h1 antagonists/ or trazodone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	202241	Advanced
16	exp anticonvulsants/ or anticonvulsant*.mp. or divalproex.mp. or topiramate.mp. or levetiracetam.mp. or zonisamide.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	228414	Advanced
17	(botox or botulinum toxin*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	24949	Advanced
18	exp complementary therapies/ or exp vitamins/ or exp dietary supplements/ or petasites.mp. or butterbur.mp. or riboflavin.mp. or ergocalciferol.mp. or magnesium.mp. or exp minerals/ [mp=title, abstract, subject headings, heading word, drug trade name, original	562444	Advanced

	title, device manufacturer, drug manufacturer, device trade name, keyword]		
19	melatonin.mp. or Melatonin/	25034	Advanced
20	biofeedback.mp. or biofeedback, psychology/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	18037	Advanced
21	electric stimulation therapy/ or transcranial magnetic stimulation/ or transcutaneous electric nerve stimulation/ or behavior therapy/ or cognitive therapy/ or mindfulness.mp. or internet.mp. or acupuncture therapy/ or acupuncture analgesia/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	195255	Advanced
22	music therapy.mp. or Music Therapy/	4180	Advanced
23	("cognitive behavior therapy" or cefaly).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2280	Advanced
24	(pizotifen or pizotyline).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1111	Advanced
25	(flunarazine or petadolex or phytotherap* or paracetamol or acetominophen).mp. [mp=title, abstract, subject headings, heading	75153	Advanced

	word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]		
26	or/4-8	490431	Advanced
27	or/10-19	1346073	Advanced
28	or/20-25	288744	Advanced
29	("case control*" or "meta analysis" or trial*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1625863	Advanced
30	exp *"headache and facial pain"/dm, dt, pc, rt, th or exp *migraine/dm, dt, pc, rt, th or (headache* or migraine*).ti.	40481	Advanced
31	30 and 26	11268	Advanced
32	30 and 27	10386	Advanced
33	30 and 28	5428	Advanced
34	or/31-33	18260	Advanced
35	limit 34 to (human and english language and yr="2003 - 2015")	9400	Advanced
36	limit 35 to (infant or child or preschool child or school child or adolescent)	964	Advanced
37	exp case control study/ or exp case study/ or exp clinical article/ or exp clinical trial/ or exp intervention study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/	3883982	Advanced
38	meta-analysis/ or systematic review/ or review.pt.	1928924	Advanced

39	comparative study/ or comparative effectiveness/ or intermethod comparison/	725779	Advanced
40	(cohort* or prospective* or retrospective* or series).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1973447	Advanced
41	or/37-40	6695419	Advanced
42	36 and 41	667	Advanced
43	30 and 9	10064	Advanced
44	limit 43 to (human and english language and yr="2003 - 2015")	5551	Advanced
45	limit 44 to (infant or child or preschool child or school child or adolescent)	662	Advanced
46	41 and 45	500	Advanced
47	42 or 46	831	Advanced
48	47 not case report/	807	Advanced
49	48 not (letter or note or short survey or editorial).pt.	790	Advanced
50	remove duplicates from 49	778	

#QueryLimiters/ExpandersLast Run ViaResultsS41S40 AND NOT S6Search modes - Boolean/PhraseInterface - EBSCOhost Research Databases

		Limiters - Published Date: 20030101-20151231; English Language Search modes -	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with	
S42	S6 OR S40	Boolean/Phrase	Full Text	525
		Search modes -	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with	
S41	S40 AND NOT S6	Boolean/Phrase	Full Text	168
		Search modes -	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with	
S40	S8 OR S13 OR S26 OR S39	Boolean/Phrase	Full Text	374
		Search modes -	Interface - EBSCOhost	
S39	S4 AND S38	Boolean/Phrase	Research Databases	67

Search Screen - Advanced Search Database - CINAHL with Full Text

	S38	S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37	**Search modes** - Boolean/Phrase	**View Results** (26,353) **View Details**
	S37	"paracetamol"	**Search modes** - Boolean/Phrase	**View Results** (801) **View Details** **Edit**
	S36	"petadolex"	**Search modes** - Boolean/Phrase	**View Results** (6) **View Details** **Edit**
	S35	"flunarazine"	**Search modes** - Boolean/Phrase	**View Results** (0) **View Details** **Edit**
	S34	"pizotifen"	**Search modes** - Boolean/Phrase	**View Results** (16) **View Details** **Edit**
	S33	(MH "Feverfew")	**Search modes** - Boolean/Phrase	**View Results** (80) **View Details**

				Edit
	S32	(MH "Transcutaneous Electric Nerve Stimulation")	**Search modes** - Boolean/Phrase	**View Results** (1,041) **View Details** **Edit**
	S31	"cefaly"	**Search modes** - Boolean/Phrase	**View Results** (4) **View Details** **Edit**
	S30	(MH "Acupuncture+") OR (MH "Acupuncture Points") OR (MH "Acupuncture Anesthesia") OR (MH "Acupuncture Analgesia")	**Search modes** - Boolean/Phrase	**View Results** (8,131) **View Details** **Edit**
	S29	(MH "Music Therapy") OR (MH "Music Therapy (Iowa NIC)")	**Search modes** - Boolean/Phrase	**View Results** (2,429) **View Details** **Edit**
	S28	(MH "Cognitive Therapy+") OR (MH "Behavior Therapy+") OR (MH "Cognitive Therapy (Iowa NIC) (Non-Cinahl)+") OR (MH "Behavior Therapy (Iowa NIC) (Non-Cinahl)+")	**Search modes** - Boolean/Phrase	**View Results** (12,492) **View Details** **Edit**
	S27	(MH "Biofeedback") OR (MH "Biofeedback (Iowa NIC)")	**Search modes** - Boolean/Phrase	**View Results** (2,102) **View Details**

				Edit
	S26	S4 AND S25	**Search modes** - Boolean/Phrase	**View Results** (254) **View Details** **Edit**
	S25	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24	**Search modes** - Boolean/Phrase	**View Results** (52,183) **View Details** **Edit**
	S24	(MH "Melatonin")	**Search modes** - Boolean/Phrase	**View Results** (1,011) **View Details** **Edit**
	S23	(MH "Magnesium")	**Search modes** - Boolean/Phrase	**View Results** (1,654) **View Details** **Edit**
	S22	(MH "Anticonvulsants+")	**Search modes** - Boolean/Phrase	**View Results** (8,626) **View Details** **Edit**
	S21	(MH "Histamine H1 Antagonists+")	**Search modes** - Boolean/Phrase	**View Results** (2,006) **View Details** **Edit**
	S20	(MH "Serotonin Uptake Inhibitors+")	**Search modes** - Boolean/Phrase	**View Results** (5,802) **View Details**

				Edit
	S19	(MH "Antidepressive Agents, Tricyclic+") OR (MH "Antidepressive Agents, Second Generation+")	**Search modes** - Boolean/Phrase	View Results (4,452) View Details Edit
	S18	(MH "Adrenergic Beta-Antagonists+") OR (MH "Adrenergic Beta-Agonists+") OR (MH "Calcium Channel Blockers+") OR (MH "Adrenergic Alpha-Antagonists+")	**Search modes** - Boolean/Phrase	View Results (16,729) View Details Edit
	S17	(MH "Dihydroergotamine")	**Search modes** - Boolean/Phrase	View Results (111) View Details Edit
	S16	(MH "Chlorpromazine")	**Search modes** - Boolean/Phrase	View Results (145) View Details Edit
	S15	(MH "Serotonin Agonists+")	**Search modes** - Boolean/Phrase	View Results (1,446) View Details Edit
	S14	(MH "Antiinflammatory Agents, Non-Steroidal+")	**Search modes** - Boolean/Phrase	View Results (16,147) View Details Edit

	S13	S4 AND S12	**Search modes** - Boolean/Phrase	View Results (142) View Details Edit
	S12	S7 OR S9 OR S10 OR S11	**Search modes** - Boolean/Phrase	View Results (137,066) View Details Edit
	S11	(MH "Vitamins+")	**Search modes** - Boolean/Phrase	View Results (23,047) View Details Edit
	S10	(MH "Alternative Therapies+")	**Search modes** - Boolean/Phrase	View Results (102,892) View Details Edit
	S9	(MH "Manual Therapy+") OR (MH "Magnet Therapy") OR (MH "Behavior Therapy+")	**Search modes** - Boolean/Phrase	View Results (38,029) View Details Edit
	S8	S4 AND S7	**Search modes** - Boolean/Phrase	View Results (12) View Details Edit
	S7	(MH "Butterbur")	**Search modes** - Boolean/Phrase	View Results (78) View Details Edit

	S6	S4 AND S5	**Search modes** - Boolean/Phrase	**View Results** (319) **View Details** **Edit**
	S5	(MH "Clinical Trials+") OR (MH "Randomized Controlled Trials") OR (MH "Study Design+")	**Limiters** - Published Date: 20030101-20151231; English Language; Age Groups: Infant, Newborn: birth-1 month, Infant: 1-23 months, Child, Preschool: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years **Search modes** - Boolean/Phrase	**View Results** (105,150) **View Details** **Edit**
	S4	S1 OR S2	**Limiters** - Published Date: 20030101-20151231; English Language; Age Groups: Infant, Newborn: birth-1 month, Infant: 1-23 months, Child, Preschool: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	**View Results** (758) **View Details** **Edit**

			Search modes - Boolean/Phrase	
	S3	S1 OR S2	**Search modes** - Boolean/Phrase	**View Results** (6,739) **View Details** **Edit**
	S2	(MH "Migraine/DH/DT/PC/PF/RT/TH")	**Search modes** - Boolean/Phrase	**View Results** (4,036) **View Details** **Edit**
	S1	(MH "Headache+/DH/DT/PC/PF/RT/TH")	**Search modes** - Boolean/Phrase	**View Results** (6,739) **View Details** **Edit**

Appendix e-4. AAN rules for classification of evidence for risk of bias

Therapeutic scheme

Class I

A randomized controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences.

The following are also required:

a. concealed allocation

b. no more than 2 primary outcomes specified

c. exclusion/inclusion criteria clearly defined

d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:

i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.

ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of

administration, dose, and dosage adjustments are similar to those previously shown to be effective).

iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.

iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.

f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate

Class II

An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b□e above (see Class I). (Alternatively, a randomized crossover trial missing 1 of the following 2 characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.) All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including studies with external controls such as well-defined natural history controls). (Alternatively, a crossover trial missing both of the following 2 criteria: period

and carryover effects described or baseline characteristics of treatment order groups presented.) A description of major confounding differences between treatment groups that could affect outcome.** Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

Class IV

Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.

*Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any 1 of the 3 is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Appendix e-5. Rules for determining confidence in evidence

- Modal modifiers used to indicate the final confidence in evidence in the conclusions
  - High confidence: highly likely or highly probable
  - Moderate confidence: likely or probable
  - Low confidence: possibly
  - Very low confidence: insufficient evidence
- Initial rating of confidence in the evidence for each intervention outcome pair
  - High: requires 2 or more Class I studies
  - Moderate: requires 1 Class I study or 2 or more Class II studies
  - Low: requires 1 Class II study or 2 or more Class III studies
  - Very low: requires only 1 Class III study or 1 or more Class IV studies
- Factors that could result in downgrading confidence by 1 or more levels
  - Consistency
  - Precision
  - Directness
  - Publication bias
  - Biological plausibility
- Factors that could result in downgrading confidence by 1 or more levels or upgrading confidence by 1 level

- Magnitude of effect
- Dose response relationship
- Direction of bias

Appendix e-6. Evidence synthesis tables

Acute Treatment

Lewis 2000 Children's ibuprofen suspension for the acute treatment of pediatric migraine	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	No; difference between groups in number receiving prophylaxis	Unclear	Yes	Yes	No	III

	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest	Adverse Effects
	Children 6-12 years with migraine N=84 Single attack study	Ibuprofen 7.5 mg/kg Placebo	Proportion of children with a headache response (severe or moderate headache reduced to mild or none) at 2 hours Ibuprofen 34/45 (76%) Placebo 21/39 (53%) P=0.006 RR 1.40 (95% CI 1.02, 2.00) Proportion of children in whom nausea was eliminated Ibuprofen 27/45 (60%) Placebo 15/39 (39%) P<0.001 RR 1.56 (95% CI 1.00, 2.51)	Not discussed in manuscript.

1

Hamalainen 1997	Masked or objective	Baseline characteristics presented	Concealed	No more than	Inclusion exclusi	Minimum 80%	Class Rating

Ibuprofen or acetaminophen for the acute treatment of migraine in children	**outcome rating**	**and equivalent**	**allocation**	**two primary outcomes specified**	**on criteria defined**	**completion rate**	
	Yes	**Yes**	**Unclear**	**Yes**	**Yes**	**Yes**	**II**
	Population N Trial Length	**Intervention and Comparator**	**Efficacy Outcomes of Interest**			**Adverse Effects**	
	Children with migraine N=88 Three attack study	**Acetaminophen 15 mg/kg Ibuprofen 10 mg/kg Placebo**	**Proportion of children with a headache response (reduction in severe or moderate headache by at least 2 grades) at 2 hours Ibuprofen 27/40 (68%) Acetaminophen 22/41 (54%) Placebo 16/43 (37%) RR (Ibuprofen vs Placebo) 1.81 (95%CI 1.18, 2.85)**			**No statistically significant difference between the number of adverse events reported 8/81 ibuprofen 4/83 acetaminophen**	

			RR (Acetaminophen vs Placebo) 1.46 (95%CI 1.03, 2.10) **Proportion of children with complete resolution (pain free) at 2 hours** **Ibuprofen 24/40 (60%)** **Acetaminophen 16/41 (39%)** **Placebo 12/43 (28%)** **RR (Ibuprofen vs Placebo) 2.15 (95%CI 1.28, 3.71)** **RR (Acetaminophen vs Placebo) 1.40 (0.77, 2.56)**	**9/81 placebo**

1

2

Winner	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcom**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**
2006 Sumatriptan nasal spray in adolescent migraineue							

rs: a randomized, double-blind, placebo-controlled acute study				**es specified**			
	Yes	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**I**
	Population N Trial Length	**Intervention and Comparator**	**Efficacy Outcomes of Interest**			**Adverse Effects**	
	Adolescents with migraine N=738 Single attack study	**Sumatriptan nasal spray 5 mg Sumatriptan nasal spray 20 mg Placebo**	**Proportion of adolescents with headache response (reduction in severity from moderate or severe to mild or no pain) at 30 minutes Placebo 80/242 (33%) 5 mg 84/247 (34%) RR 1.03 (0.80,1.32) 20 mg 99/236 (42%) RR 1.27 (1.01, 1.60)** **Proportion of adolescents with headache response (reduction in severity from**			**At least one drug related adverse effect Placebo 15/245 (6%) 5 mg 59/255 (23%) 20 mg 76/238 (32%)** **No serious adverse effects or withdrawal**	

			moderate or severe to mild or no pain) at 60 minutes **Placebo 126/242 (52%)** **5 mg 131/247 (53%) RR 1.02 (0.86, 1.21)** **20 mg 144/236 (61%) RR 1.17 (1.00, 1.37)** **Proportion of adolescents with headache response (reduction in severity from moderate or severe to mild or no pain) at 120 minutes** **Placebo 140/242 (58%)** **5 mg 156/247 (63%) RR 1.09 (0.95, 1.26)** **20 mg 160/236 (68%) RR 1.17 (1.02, 1.35)** **Proportion of adolescents who were pain free at 2 hours** **Placebo 73/242 (30%)**	**due to an adverse effect** **The most common adverse effect was taste disturbance.**

			20 mg 104/236 (44%) RR 1.46 (1.15, 1.86) **Proportion of adolescents without photophobia and phonophobia at 2 hours post dose** **Placebo 173/244** **5 mg 191/248 RR 1.09 (0.98, 1.21)** **20 mg 188/237 RR 1.12 (1.01, 1.24)** **Proportion of adolescents without nausea at 2 hours post dose** **Placebo 196/244** **5 mg 203/248 RR 1.02 (0.94, 1.11)** **20 mg 195/237 RR 1.02 (0.94, 1.11)**	

			Proportion of adolescents without vomiting at 2 hours post dose **Placebo 236/244** **5 mg 245/248 RR 1.02 (0.99. 1.06)** **20 mg 233/237 RR 1.02 (0.99, 1.05)**	

1

Winner 2000 **A randomized double-blind placebo-controlled study of sumatriptan nasal spray in the treatment**	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcomes specified**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**
	Yes	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**II**
	Population **N**	**Intervention and Comparator**	**Efficacy Outcomes of Interest**			**Adverse Effects**	

of acute migraine in adolescents	**Trial Length**			
	Adolescents with migraine N=510 Single attack study	**Sumatriptan nasal spray 5 mg, 10 mg, and 20 mg Placebo**	**Proportion of adolescents with headache relief (reduction in headache pain from moderate or severe to mild or no pain) at one hour** **Placebo 54/131** **5 mg 60/128 RR 1.05 (0.87, 1.50)** **10 mg 74/133 RR 1.35 (1.05, 1.74)** **20 mg 66/118 RR 1.36 (1.05, 1.76)** **Proportion of adolescents with headache relief (reduction in headache pain from moderate or severe to mild or no pain) at two hours** **Placebo 69/131** **5 mg 84/128 RR 1.25 (1.02, 1.53)**	**Taste disturbance was the most commonly reported adverse event.** **When taste disturbance was not included, the overall incidence of adverse events was similar in the sumatriptan and placebo treatment groups.**

			10 mg 85/133 RR 1.21 (0.99, 1.50) **20 mg 74/118 RR 1.25 (1.06, 1.48)** **Proportion of adolescents who had complete relief at 2 hours** **Placebo 33/131** **20 mg 42/118 RR 1.45 (0.99, 2.11)** **Proportion of adolescents without nausea at 2 hours** **Placebo 98/131** **5 mg 102/128 RR 1.07 (0.93, 1.22)** **10 mg 110/133 RR 1.11 (0.97, 1.26)** **20 mg 93/118 RR 1.05 (0.92, 1.21)**	

			Proportion of adolescents without vomiting at 2 hours **Placebo 124/131** **5 mg 119/128 RR 0.98 (0.92, 1.05)** **10 mg 126/133 RR 1.00 (0.94, 1.07)** **20 mg 112/118 RR 1.00 (0.94, 1.07)** **Proportion of adolescents without photophobia at 2 hours** **Placebo 68/131** **5 mg 79/128 RR 1.19 (0.96, 1.48)** **10 mg 76/133 RR 1.10 (0.88, 1.37)** **20 mg 76/118 RR 1.24 (1.004, 1.54)**	

			Proportion of adolescents without phonophobia at 2 hours **Placebo 73/131** **5 mg 92/128 RR 1.29 (1.07, 1.56)** **10 mg 89/133 RR 1.20 (0.99, 1.46)** **20 mg 88/118 1.34 (1.11, 1.62)**	

1

Ahonen 2004 Nasal sumatriptan is effective in treatment of migraine	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcomes specified**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**
	Yes	**Yes**	**No**	**Yes**	**Yes**	**No**	**II**

attacks in children	**Population** **N** **Trial Length**	**Intervention and Comparator**	**Efficacy Outcomes of Interest**	**Adverse Effects**
	Children 8-17 years with migraine **N=94** **2 attack study**	**Crossover; subjects treated one attack each with placebo and sumatriptan nasal spray 10 mg or 20 mg depending on weight**	**Proportion of children with headache relief (from severe or moderate to mild or no pain) at one hour** **Placebo 24/83** **10 mg 16/28 RR 1.98 95% CI 1.21, 3.05** **20 mg 26/55 RR 1.63 95% CI 1.05, 2.51** **Proportion of children with headache relief (from severe or moderate to mild or no pain) at two hours** **Placebo 27/83** **10 mg 18/28 RR 1.98 95%CI 1.27, 2.91**	**No serious adverse effects were observed. Bad taste of the medication was the most common complaint.**

			20 mg 35/55 RR 1.96 95%CI 1.35, 2.82 **Proportion of children who were pain free at 2 hours** **Placebo 17/83** **10 mg 9/28 RR 1.57 95%CI 0.78, 2.96** **20 mg 17/55 RR 1.51 95%CI 0.85, 2.65**	

Fujita 2014 Oral sumatriptan for migraine in children and adolescents: a randomized multicenter placebo controlled parallel group study	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	Children and adolescents 10-17 years with migraine	Placebo Sumatriptan 25 mg tablet Sumatriptan 50 mg tablet	Proportion of children with pain relief (2 point reduction on a 5 point scale) at 30 minutes Placebo 3/70 Sumatriptan 25 mg 0/33 RR 0.35 (0.03, 4.20)			Overall incidence of adverse effects 25 mg 15% 50 mg 17% Placebo 14% No serious adverse effects;	

	N=178 **Single attack study**		**Sumatriptan 50 mg 4/41 RR 2.27 (0.57, 8.77)** **Proportion of children with pain relief (2 point reduction on a 5 point scale) at 60 minutes** **Placebo 13/70** **Sumatriptan 25 mg 3/33 RR 0.49 (0.16, 1.46)** **Sumatriptan 50 mg 3/41 RR 0.39 (0.13, 1.20)** **Proportion of children with pain relief (2 point reduction on a 5 point scale) at 120 minutes** **Placebo 27/70** **Sumatriptan 25 mg 11/33 RR 0.86 (0.48, 1.46)** **Sumatriptan 50 mg 12/41 RR 0.76 (0.43, 1.29)**	**no adverse event related withdrawls**

			Proportion of children who were pain free at 120 minutes **Placebo 20/70** **Sumatriptan 25 mg 8/33 RR 0.85 (0.42, 1.64)** **Sumatriptan 50 mg 8/41 RR 0.68 (0.33, 1.35)** **Percentage of patients who were free of photophobia at 2 hours** **Sumatriptan (pooled) 53.6%** **Placebo 52.8% p=0.95** **Percentage of patients who were free of phonophobia at 2 hours** **Sumatriptan (pooled) 53.3%** **Placebo 63.6%** **Percentage of patients who were free of nausea** **Sumatriptan (pooled) 61.1%**	

			Placebo 81.0%	

1

Hamalainen 1997 Sumatriptan for migraine attacks in children: a randomized placebo-controlled study	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcomes specified**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**
	Yes	**Presented but not equivalent**	**Unclear**	**Yes**	**Yes**	**No**	**III**
	Population N Trial Length	**Intervention and Comparator**	**Efficacy Outcomes of Interest**			**Adverse Effects**	

	Children 8-16 years with migraine N=23 2 attack crossover study	**Placebo Sumatriptan 50 or 100 mg tablet (depending on body surface area)**	**Proportion of children with 50% reduction in pain intensity at 2 hours Placebo 5/23 Sumatriptan 7/23 RR 1.40 (0.55, 3.62)**	

1

Desrosier 2012 Randomized trial of sumatriptan and naproxen sodium combination in	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcomes specified**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**
	Yes	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**I**

adolescent migraine	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest	Adverse Effects
	12-17 year olds with migraine N=490 Single attack study	Placebo Sumatriptan/ naproxen 10/60 mg Sumatriptan/ naproxen 30/180 mg Sumatriptan/ naproxen 85/500 mg	Proportion of adolescents who were pain free at 2 hours Placebo 14/142 10/60 mg 28/96 RR 2.96 (1.65-5.26) 30/180 mg 26/97 RR 2.72 (1.51-4.88) 85/500 mg 36/150 RR 2.43 (1.39-4.29) Proportion of adolescents who were photophobia free at 2 hours Placebo 59/144 10/60 mg 57/96 RR 1.45 (1.12-1.87)	Treatment emergent adverse events 10/60 mg 13% 30/180 mg 9% 85/500 mg 13% placebo 8% Most common adverse events were nasopharyngitis, hot flush and muscle tightness.

			30/180 mg 47/96 RR 1.19 (0.90-1.58) **85/500 mg 89/151 RR 1.44 (1.14-1.83)** **Proportion of adolescents who were phonophobia free at 2 hours** **Placebo 60/144** **10/60 mg 58/96 RR 1.45 (1.12-1.86)** **30/180 mg 55/96 RR 1.38 (1.06-1.77)** **85/500 mg 90/151 RR 1.43 (1.14-1.81)** **Proportion of adolescents who were nausea free at 2 hours** **Placebo 101/144** **10/60 mg 78/95 RR 1.17 (1.01-1.35)**	

			30/180 mg 74/96 RR 1.10 (0.94-1.28) **85/500 mg 106/151 RR 1.00 (0.86-1.16)**	

Evidence Summary Tables

Winner 2015	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcomes specified**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**
	Yes	**Crossover study**	**Unclear**	**No**	**Yes**	**Yes**	**II**
	Population **N**	**Intervention and Comparator**	**Efficacy Outcomes of Interest**			**Adverse Effects**	

	Trial Length			
	Adolescents 12-17 with migraine **N=94** **4 attack crossover study**	**Sumatriptan / naproxen 85/500 mg** **Placebo**	**Proportion of migraines in which adolescents were pain free at 2 hours** **Sumatriptan/naproxen 102/277** **Placebo 13/70** **RR 1.98 (1.22-3.35)**	**Incidence of adverse events** **Sumatriptan naproxen 30/277 (10.8%)** **Placebo 2/70 (3%)** **Most common adverse effects: neck spasm/tension, drowsiness, throat tightness, jaw tightness, dizziness, shoulder tightness, nausea**

1

2

Winner 2002 Rizatriptan 5 mg for the acute treatment of migraine in adolescents: a randomized, double-blind placebo controlled study	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcomes specified**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**
	Yes	**Yes**	**Unclear**	**Yes**	**Yes**	**Yes**	**II**
	Population N Trial Length	**Intervention and Comparator**	**Efficacy Outcomes of Interest**			**Adverse Effects**	
	Adolescents 12-17 with migraine N=296 Up to three	**Rizatriptan 5 mg Placebo**	**Proportion of adolescents who were pain free at 2 hours Rizatriptan 48/149 Placebo 40/142 RR 1.14 (0.81-1.62)**			**Any drug related adverse events Rizatriptan 22.1% Placebo 23.8% Most common adverse events**	

	migraine attacks		**Proportion of adolescents with pain relief (mild or no pain) at 2 hours** **Rizatriptan 98/149** **Placebo 80/142 RR 1.17 (0.97-1.41)** **Proportion of adolescents who were free of nausea at 1 hour** **Rizatriptan 110/149** **Placebo 90/142 RR 1.16 (1.00-1.37)** **No difference in photophobia at any time point (raw data not provided)** **Proportion of adolescents who were free of phonophobia at 30 minutes** **Rizatriptan 52/149** **Placebo 65/142 RR 0.76 (0.57-1.01)**	**Rizatriptan: asthenia (3.4%), dizziness (4.7%), dry mouth (4.7%) None significantly differently from placebo.** **Placebo: Nausea (8.2%), somnolence (8.2%). Both significantly higher than in rizatriptan group.**

			Proportion of adolescents who were free of phonophobia at 2 hours Rizatriptan 104/149 Placebo 98/142 RR 1.01 (0.87-1.18)	

1

Visser 2004 Rizatriptan 5 mg for the acute treatment of migraine in adolescents: results from a double blind,	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcomes specified**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**
	Yes	**Yes**	**No**	**Yes**	**Yes**	**No**	**II**
	Population N	**Intervention and Comparator**	**Efficacy Outcomes of Interest**			**Adverse Effects**	

single attack	**Trial Length**			
study and two open label, multiple attack studies	**Adolescents 12-17 with migraine N=476 Single attack study; up to two recurrences**	**Rizatriptan 5 mg Placebo**	**Proportion of adolescents who had pain relief (from severe or moderate to mild or no pain) at 2 hours Rizatriptan 5 mg 159/233 Placebo 165/240 RR 0.99 (0.88-1.12)** **Proportion of adolescents who were pain free at 2 hours Rizatriptan 91/233 Placebo 75/240 RR 1.25 (0.98-1.60)** **No statistically significant difference between treatment groups in any of the associated symptoms at any time point (raw data not given)**	**Percentage of patients with drug-related clinical adverse events Rizatriptan 20.1% Placebo 16.5% Most common adverse events Somnolence Rizatriptan 8.1% Placebo 5.8% Dizziness Rizatriptan 7.7% Placebo 4.1% Dry mouth Rizatriptan 5.1% Placebo 2.1% Nausea Rizatriptan 4.7%**

				Placebo 5.4%

1

Ho 2012 Efficacy and tolerability of rizatriptan in pediatric migraine: results from a randomized, double-blind placebo controlled trial using a novel adaptive	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcomes specified**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**
	Yes	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**II**
	Population N Trial Length	**Intervention and Comparator**	**Efficacy Outcomes of Interest**			**Adverse Effects**	
	Children 6-17 years with migraine and	**Rizatriptan 5 or 10 mg (depending on weight) Placebo**	**Proportion of children who were pain free at 2 hours Rizatriptan 126/382 Placebo 94/388 RR 1.36 (1.09-1.71)**			**Drug-related adverse events Rizatriptan 12.1% Placebo 11.3%**	

enrichment design	**unsatisfactory response to NSAIDs or acetaminophen N=770 Single attack study, 2 stage study with stage 1 to identify placebo non-responders, who went on to Stage 2**		**Proportion of children who had pain relief (from moderate or severe to mild or no pain) at 2 hours Rizatriptan 220/382 Placebo 204/388 RR 1.10 (0.96-1.25)** **Proportion of children who had no photophobia at 2 hours Rizatriptan 235/382 Placebo 216/388 RR 1.11 (0.98-1.25)** **Proportion of children who had no phonophobia at 2 hours Rizatriptan 254/382 Placebo 233/388 RR 1.11 (0.99-1.23)**	**Most common adverse events Rizatriptan Somnolence 2.8% Nausea 2.6% Fatigue 2.8% Placebo Somnolence 2.5% Nausea 2.5% Dizziness 3.7%**

			Proportion of children who had no nausea at 2 hours **Rizatriptan 329/381** **Placebo 303/388 RR 1.11 (1.04-1.18)** **Proportion of children who had no vomiting at 2 hours** **Rizatriptan 373/381** **Placebo 372/388 RR 1.02 (0.99-1.05)**	

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2

Linder 2008 Efficacy and tolerability of almotriptan in	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcomes**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**

adolescents: a randomized, double-blind, placebo-controlled trial				**specified**			
	Yes	**Yes**	**Unclear**	**Yes**	**Yes**	**Yes**	**II**
	Population N Trial Length	**Intervention and Comparator**	**Efficacy Outcomes of Interest**			**Adverse Effects**	
	Adolescents 12-17 with migraine N=866 Single attack study	**Almotriptan 6.25 mg, 12.5 mg or 25 mg Placebo**	**Proportion of adolescents with pain relief (decrease from moderate or severe to mild or no pain) at 2 hours Placebo 94/170 6.25 mg 127/177 RR 1.30 (1.10-1.53) 12.5 mg 132/181 RR 1.32 (1.13-1.56) 25 mg 124/186 RR 1.21 (1.02-1.43) Proportion of adolescents who were pain free at 2 hours**			**The proportion of patients with one or more adverse effect Placebo 18.6% 6.25 mg 15.0% 12.5 mg 23.6% 25 mg 25.8% Most common adverse effects: Dizziness, somnolence, nausea**	

			Placebo 58/170 **6.25 mg 63/177 RR 1.04 (0.78-1.39)** **12.5 mg 74/181 RR 1.20 (0.91-1.57)** **25 mg 75/186 RR 1.18 (0.90-1.55)** **No significant differences in the incidence of nausea, photophobia or phonophobia at 2 hours between the 25 mg and placebo groups; further analyses of other dosages not performed.**	

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Winner 2007	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcom**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**
Eletriptan for the acute treatment of							

migraine in adolescents: results of a double-blind, placebo controlled trial				**es specified**			
	Yes	**Yes**	**Unclear**	**Yes**	**Yes**	**No**	**II**
	Population **N** **Trial Length**	**Intervention and Comparator**	**Efficacy Outcomes of Interest**			**Adverse Effects**	
	Adolescents 12-17 with migraine **N=267** **Single attack study**	**Eletriptan 40 mg** **Placebo**	**Proportion of adolescents with headache response (from moderate or severe to mild or no pain) at 2 hours** **Eletriptan 80/141** **Placebo 76/133 RR 0.99 (0.81-1.22)** **Proportion of adolescents who were pain free at 2 hours** **Eletriptan 31/141** **Placebo 20/133 RR 1.46 (0.88-2.42)**			**Most common adverse effects Somnolence, dizziness, asthenia, nausea** **No serious treatment related adverse events in either group.**	

			Proportion of adolescents who were free of nausea at 2 hours **Eletriptan 106/141** **Placebo 104/133 RR 0.96 (0.84-1.10)** **Proportion of adolescents who were free of photophobia at 2 hours** **Eletriptan 87/141** **Placebo 85/133 RR 0.97 (0.80-1.16)** **Proportion of adolescents who were free of photophobia at 2 hours** **Eletriptan 99/141** **Placebo 89/133 RR 1.05 (0.89-1.24)**	

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Lewis 2007 Efficacy of zolmitriptan nasal spray in adolescent migraine	**Masked or objective outcome rating**	**Baseline characteristics presented and equivalent**	**Concealed allocation**	**No more than two primary outcomes specified**	**Inclusion exclusion criteria defined**	**Minimum 80% completion rate**	**Class Rating**
	Yes	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**II**
	Population **N** **Trial Length**	**Intervention and Comparator**	**Efficacy Outcomes of Interest**			**Adverse Effects**	
	Adolescents 12-17 years with migraine N=248	**Zolmitriptan 5 mg nasal spray** **Placebo**	**Proportion of adolescents with headache response (improvement in headache by 2 points on a 4 point scale) at 1 hour** **Zolmitriptan 86/148**			**Drug related adverse events** **Placebo 17/184** **Zolmitriptan 32/200**	

	2 attack crossover study		**Placebo 55/127 RR 1.34 (1.06-1.71)** **Proportion of adolescents with 2-hour sustained headache response** **Zolmitriptan 76/148** **Placebo 42/127 RR 1.55 (1.17-2.09)** **Proportion of adolescents who were pain free at one hour** **Zolmitriptan 41/148** **Placebo 13/127 RR 2.71 (1.54-4.79)** **Proportion of adolescents who were pain free at two hours** **Zolmitriptan 58/148** **Placebo 24/127 RR 2.07 (1.39-3.13)**	**Most common adverse events** **Taste disturbance** **Placebo 5/184** **Zolmitriptan 13/200** **Nasal discomfort** **Placebo 2/184** **Zolmitriptan 5/200**

			Proportion of adolescents who were free of photophobia at 30 minutes **Zolmitriptan 37/114** **Placebo 19/97 RR 1.66 (1.03-2.68)** **Proportion of adolescents who were free of phonophobia at 30 minutes** **Zolmitriptan 32/89** **Placebo 18/84 RR 1.68 (1.03-2.74)**	

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Winner 2016	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating

				specified			
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	Adolescents 12-17 years with migraine; placebo non-responders N=798 Single attack study	Zolmitriptan nasal spray 0.5, 2.5 and 5 mg Placebo	Proportion of adolescents who were pain free at 2 hours Zolmitriptan nasal spray 5 mg 68/229 Placebo 42/253 RR 1.79 (1.28-2.51) Proportion of adolescents with a headache response at 2 hours Zolmitriptan nasal spray 5 mg 116/229 Placebo 99/253 RR 1.29 (1.06-1.58)			No serious adverse effects or adverse effects leading to discontinuation were reported. Dysgeusia was most frequently reported. No clinically meaningful differences observed in vital signs, hematology, clinical chemistry,	

			No statistically significant reduction in the occurrence of nausea or vomiting was seen for zolmitriptan nasal spray 5 mg (data not provided in manuscript) **Proportion of adolescents without photophobia at 2 hours** **Zolmitriptan nasal spray 5 mg 123/219** **Placebo 110/247** **RR 1.26 (1.05-1.51)** **Proportion of adolescents without phonophobia at 2 hours** **Zolmitriptan nasal spray 5 mg 128/219** **Placebo 119/247** **RR 1.21 (1.02-1.44)**	**urinalysis or ECG parameters.**

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Appendix e-7. Steps and rules for formulating recommendations

Constructing the recommendation and its rationale

Rationale for recommendation summarized in the rationale includes 3 categories of premises

- Evidence-based conclusions for the systematic review
- Stipulated axiomatic principles of care
- Strong evidence from related conditions not systematically reviewed

Actionable recommendations include the following mandatory elements

- The patient population that is the subject of the recommendation
- The person performing the action of the recommendation statement
- The specific action to be performed
- The expected outcome to be attained

Assigning a level of obligation

Modal modifiers used to indicate the final level of obligation (LOO)

- Level A: Must

- Level B: Should
- Level C: May
- Level U: No recommendation supported

LOO assigned by eliciting panel members' judgments regarding multiple domains, using a modified Delphi process. Goal is to attain consensus after a maximum of 3 rounds of voting. Consensus is defined by:

- > 80% agreement on dichotomous judgments
- >80% agreement, within 1 point for ordinal judgments
- If consensus obtained, LOO assigned at the median. If not obtained, LOO assigned at the 10th percentile

Three steps used to assign final LOO

1. Initial LOO determined by the cogency of the deductive inference supporting the recommendation on the basis of ratings within 4 domains. Initial LOO anchored to lowest LOO supported by any domain.

   - Confidence in evidence. LOO anchored to confidence in evidence determined by modified form of the Grading of Recommendations Assessment, Development and Evaluation process

- Level A: High confidence
- Level B: Moderate confidence
- Level C: Low confidence
- Level U: Very low confidence

 Soundness of inference assuming all premises are true. LOO anchored to proportion of panel members convinced of soundness of the inference

- Level A: 100%
- Level B: ≥ 80% to < 100%
- Level C: ≥ 50% to < 80%
- Level U or R: < 50%

 Acceptance of axiomatic principles: LOO anchored to proportion of panel members who accept principles

- Level A: 100%
- Level B: ≥ 80% to < 100%
- Level C: ≥ 50% to < 80%
- Level U or R: < 50%

 Belief that evidence cited from rerated conditions is strong: LOO anchored to proportion of panel members who believe the related evidence is strong

- Level B: ≥ 80% to 100% (recommendations dependent on inferences from nonsystematically reviewed evidence cannot be anchored to a Level A LOO)
- Level C: ≥ 50% to < 80%
- Level U or R: < 50%

2. LOO is modified mandatorily on the basis of the judged magnitude of benefit relative to harm expected to be derived from complying with the recommendation

- Magnitude relative to harm rated on 4-point ordinal scale
  - Large benefit relative to harm: benefit judged large, harm judged none
  - Moderate benefit relative to harm: benefit judged large, harm judged minimal; or benefit judged moderate, harm judged none
  - Small benefit relative to harm: benefit judged large, harm judged moderate; or benefit judged moderate, harm judged minimal; or benefit judged small, harm judged none
  - Benefit to harm judged too close to call: benefit and harm judged to be substantially similar
- Regardless of cogency of the recommendation the LOO can be no higher than that supported by the rating of the magnitude of benefit relative to harm
  - Level A: large benefit relative to harm
  - Level B: moderate benefit relative to harm

- Level C: small benefit relative to harm
- Level U: too close to call

 LOO can be increased by one grade if LOO corresponding to benefit relative to harm greater than LOO corresponding to the cogency of the recommendation

3. LOO optionally downgraded on the basis of the following domains

 Importance of the outcome: critical, important, mildly important, not important

 Expected variation in patient preferences: none, minimal, moderate, large

 Financial burden relative to benefit expected: none, minimal, moderate, large

 Availability of intervention: universal, usually, sometimes, limited

The rationale profiles shown in appendix e-8 summarize the results of panel ratings for each domain described above. The profiles also indicate the corresponding assigned LOOs. The last column in each indicates whether consensus was obtained for that domain.

Appendix e-8. Rationale of factors considered in developing the practice recommendations

Recommendation 1 Rationale

The appropriate care of a patient with headaches requires establishing a correct diagnosis [PRIN]. This affects our diagnostic approach, treatment, and prognosis. Headaches may be classified as primary (migraine, tension-type, trigeminal autonomic cephalalgia), secondary (related to another condition [e.g., infection, trauma, tumor]), or other headache syndromes (painful cranial neuropathies, facial pain, and other headache) [PRIN].[4] Patients with signs and symptoms of secondary headache, such as sudden change in headache, papilledema, focal deficits, and the additional presence of seizures, require further evaluation beyond a thorough history and physical examination. When migraine is diagnosed, tailored treatments may be considered that can result in improved outcomes and quality of life [RELA].[24] Diagnostic criteria for pediatric migraine include at least five headaches over the past year that last 2-72 hours when untreated, with two of four additional features (pulsatile quality, unilateral or, worsening with activity or limiting activity, moderate to severe in intensity), and association with at least nausea or vomiting, or photophobia and phonophobia. These associated symptoms can be inferred by family report of the child's activities. The time a child sleeps can be considered part of the headache duration. Auras typically occur in about one third of older children and adolescents and precede the headache by 5-60 minutes [PRIN].[4]

Statement 1a

When evaluating children and adolescents with headache, clinicians should diagnose a specific headache type (primary, secondary, or other headache syndrome) (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 1	Mildly Important 0	Very important 7	Critically important 6	Yes
Variation in preferences	Large 0	Moderate 0	Modest 4	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 6	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 6	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1b

When evaluating children and adolescents with headache, clinicians should ask about premonitory and aura symptoms, headache semiology (onset, location, quality, severity, frequency, duration, aggravating and alleviating factors), associated symptoms (nausea, vomiting, phonophobia, and photophobia), and pain-related disability in order to improve diagnostic accuracy for migraine and appropriately counsel the patient (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 8	Critically important 6	Yes
Variation in preferences	Large 0	Moderate 0	Modest 4	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 2 Rationale

Migraine treatment should aim to achieve fast, complete pain relief, with minimum side effects [PRIN]. Associated symptoms like nausea, vomiting, photophobia, and phonophobia should also be addressed. In adults, early treatment of migraine (within less than one hour of headache onset) improves pain-free rates [RELA].[25] Improved efficacy with early treatment is likely to be seen in children and adolescents as well [INFER]. Many children and adolescents use and benefit from

nonprescription oral analgesics like acetaminophen, ibuprofen, and naproxen [RELA].[26] Triptans are less commonly prescribed in children than in adults, and only almotriptan OT (for patients aged 12 years and older), rizatriptan ODT (for patients aged 6-17 years), sumatriptan/naproxen OT (for patients aged 12 years and older), and zolmitriptan NS (for patients aged 12 years and older) are approved by the Food and Drug Administration (FDA) for use in children. Ergots and oral naproxen alone have not been studied in children.

Statement 2a

Clinicians should counsel that acute migraine treatments are more likely to be effective when used earlier in the migraine attack, when pain is still mild (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 9	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 1	Modest 8	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 7	Small 7	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Statement 2b

Clinicians should prescribe ibuprofen OS (10 mg/kg) as an initial treatment option to reduce pain in children and adolescents with migraine (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 9	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 1	Modest 7	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 11	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 10	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Statement 2c

For adolescents with migraine, clinicians should prescribe sumatriptan/naproxen OT (10/60 mg, 30/180 mg, 85/500 mg), zolmitriptan NS (5 mg), sumatriptan NS (20 mg), rizatriptan ODT (5 mg or 10 mg), or almotriptan OT (6.25 mg or 12.5 mg) to reduce headache pain (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 5	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 9	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 8	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 1	Usually 9	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 10	Small 3	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Recommendation 3 Rationale

Patients respond differently to the same medication [PRIN]. In adults, failure to respond to one triptan does not preclude response to an alternate triptan [RELA].[27] In adults who respond to a triptan but have recurrence of their headache within 24 hours, taking a second dose is effective [RELA].[28] Children might have the same experience [INFER], but product monograph daily maximum doses must be followed [PRIN]. Migraine features (severity, associated symptoms, disability, and most bothersome symptoms) differ among individuals and among different attacks

in the same individual [RELA].[29] Intranasal sumatriptan and zolmitriptan are absorbed more quickly than the oral form [RELA][30, 31] and has a faster onset of action [RELA].[32, 33] For migraines that rapidly peak in severity or are associated with nausea and vomiting, non-oral forms of treatment may be more effective [INFER]. Thus, children with migraine may benefit from more than one acute treatment choice and different delivery routes, depending on their individual headache characteristics [INFER].

Statement 3a

Clinicians should counsel patients and families that a series of medications may need to be used to find treatments that most benefit the patient (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 9	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 1	Modest 9	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 2	Usually 7	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 10	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Statement 3b

Clinicians should instruct patients and families to use the medication that best treats the characteristics of each migraine to provide the best balance of efficacy, side effects, and patient preference (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 9	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 9	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 8	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 9	Small 5	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Statement 3c

Clinicians should offer an alternate triptan, if 1 triptan fails to provide pain relief, to find the most effective agent to reduce migraine symptoms (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 6	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 11	Critically important 3	Yes
Variation in preferences	Large 1	Moderate 0	Modest 8	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 1	Usually 8	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 9	Small 4	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Statement 3d

Clinicians may prescribe a nonoral route when headache peaks in severity quickly, is accompanied by nausea and/or vomiting, or oral formulations fail to provide pain relief (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 5	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 10	Critically important 4	Yes
Variation in preferences	Large 1	Moderate 4	Modest 7	Minimal 2	No
Feasible	Rarely 0	Occasionally 2	Usually 9	Always 3	Yes
Cost relative to net benefit	Very large 0	Large 2	Moderate 8	Small 4	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Statement 3e

Clinicians should counsel patients and families that if their headache is successfully treated by their acute migraine medication but headache recurs within 24 hours of their initial treatment, taking a second dose of acute migraine medication can treat the recurrent headache (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 10	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 1	Modest 6	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 8	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 4 Rationale

Sumatriptan/naproxen OT (10/60 mg, 30/180 mg, and 85/500 mg tablet) is more likely than placebo to result in headache pain-free status at 2 hours [EVID]. Sumatriptan and naproxen have a different pharmacokinetic profiles targeted to aid in migraine relief [RELA].[34] In adults, the sumatriptan/naproxen combination OT is more effective than monotherapy with either component [RELA].[35] Because of cost and insurance issues, not all patients have access to all available formulations of medications [PRIN]. Given the distinct mechanisms of action among

medications in the triptan class and the NSAID class [PRIN], the addition of an NSAID to a triptan may improve rates of pain response and pain-free status [INFER].

Statement 4

In adolescents whose migraine is incompletely responsive to a triptan, clinicians should offer ibuprofen or naproxen in addition to a triptan to improve migraine relief (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 7	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 9	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 2	Modest 7	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 7	Small 7	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Recommendation 5 Rationale

Migraine is typically accompanied by other symptoms (nausea, vomiting, photophobia, phonophobia) in addition to head pain [PRIN]. Anti-emetics are often prescribed along with specific (triptan) and nonspecific (NSAID) migraine treatments to address nausea and vomiting and to speed the rate of medication absorption [PRIN]. In pediatric migraine trials, the treatment effects on migraine-associated symptoms were less pronounced than the treatment effects on

pain [EVID]. While photophobia and phonophobia were responsive to zolmitriptan nasal spray and sumatriptan/naproxen [EVID], none of the treatments studied had demonstrated effectiveness against nausea or vomiting [EVID]. Antiemetics are available to treat nausea and vomiting related to other pediatric conditions (acute gastroenteritis, postoperative state, chemotherapy) [RELA][36, 37] and may be of benefit for migraine-associated nausea, although no clinical trials specifically evaluating anti-emetics for pediatric migraine-associated nausea have been performed [INFER]. Nasal spray formulations of zolmitriptan and sumatriptan may be easier to administer in adolescents with migraine with prominent nausea and/or vomiting [PRIN].

Statement 5

For children and adolescents with migraine who experience prominent nausea and/or vomiting, clinicians should offer additional anti-emetic treatments (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 4	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 11	Critically important 3	Yes
Variation in preferences	Large 1	Moderate 1	Modest 7	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 9	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 8	Small 5	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Recommendation 6 Rationale

Patient education can improve patient safety and adherence to interventions [PRIN]. It is important to learn about the behavioral aspects of self-care that might improve migraine, including healthy habits with lifestyle modification, potential migraine triggers/aggravating factors, and the risk of overusing medication [INFER]. Maintaining a headache diary is helpful to track response to any new therapy. Patients and families will benefit from understanding the

limitations of current available treatments [INFER]. Overuse of medication to treat acute attacks has been associated with medication overuse headache in adults [RELA][38] but has not been well-studied in children. Methods to prevent medication overuse headache are included in adult treatment plans [PRIN].

Statement 6a

Clinicians should counsel children and adolescents with migraine and their families about migraine-healthy habits, including lifestyle modification, and identification/disproving/resolution of migraine triggers/aggravating factors and avoidance of medication overuse (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 2	Modest 8	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 6b

Clinicians should make collaborative agreements with children and adolescents with migraine and their families on treatment goals that are individualized to the patient (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 1	Mildly Important 0	Very important 8	Critically important 5	Yes
Variation in preferences	Large 1	Moderate 0	Modest 7	Minimal 6	Yes
Feasible	Rarely 1	Occasionally 1	Usually 2	Always 10	Yes
Cost relative to net benefit	Very large 1	Large 0	Moderate 1	Small 12	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Statement 6c

Clinicians may counsel children and adolescents with migraine and their families to maintain a headache diary to monitor their response to treatments (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 1	Mildly Important 1	Very important 6	Critically important 6	Yes
Variation in preferences	Large 1	Moderate 6	Modest 3	Minimal 4	No
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 0	Small 14	Yes
Strength of recommendation	R/U	C	B	A	

Statement 6d

6d. Clinicians should counsel patients and families to use no more than 14 days of ibuprofen or acetaminophen per month, no more than 9 days of triptans per month, and no more than 9 days per month of any combination of triptans, analgesics or opioids** for more than three months to avoid medication overuse headache (Level B).

**There is no evidence to support the use of opioids in children with migraine – opioids are included in this statement to be consistent with the International Classification of Headache Society Disorders 3rd edition regarding medication overuse.

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 13	Critically important 2	Yes
Variation in preferences	Large 0	Moderate 0	Modest 9	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 13	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 7 Rationale

According to the FDA, triptans are contraindicated in patients with a history of cardiovascular disease, including stroke, transient ischemic attacks, myocardial infarction, severe peripheral vascular disease, ischemic bowel disease, and coronary vasospasm, including Prinzmetal angina. Triptans are also contraindicated in patients with cardiac accessory conduction pathway disorders, including Wolff-Parkinson-White syndrome [PRIN]. Although the 2004 American Headache Society consensus statement does not consider these as absolute contraindications,[39] these contraindications (INFER) are based on the known pharmacology of the triptans[40] and triptan effects on vascular muscle [RELA].[41] While these medical contraindications are less prevalent in the pediatric population, they are important to consider.

Statement 7

Clinicians must not prescribe triptans to those with a history of ischemic vascular disease or accessory conduction pathway disorders to avoid the morbidity and mortality associated with aggravating these conditions (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 5	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 6	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 1	Modest 5	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 8 Rationale

In adults who have migraine with typical aura, there is evidence that it is safe to take triptans during the aura, although the triptan may be more effective if taken at the onset of pain [RELA].[42, 43] The use of triptans during the aura phase is of concern because of potential difficulties differentiating early stroke symptoms from migraine aura [PRIN]. While this is unlikely a problem in those with established migraine with visual aura, caution is warranted in

those with more complex aura presentations [PRIN]. According to the FDA, triptans are contraindicated in those with a history of hemiplegic aura or migraine with brainstem aura [PRIN]. This contraindication was based on a view of migraine pathophysiology that is no longer considered current.

Statement 8a

Clinicians should counsel adolescent patients with migraine with aura that taking their triptan during a typical aura is safe, but that the triptan may be more effective if taken at the onset of head pain (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 6	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 1	Mildly Important 0	Very important 12	Critically important 2	Yes
Variation in preferences	Large 1	Moderate 1	Modest 6	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation Statement 8b

Clinicians may consider referral of children and adolescents with hemiplegic migraine or migraine with brainstem aura who do not respond to other treatments to a headache specialist to find effective treatment (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 8	Critically important 6	Yes
Variation in preferences	Large 0	Moderate 1	Modest 6	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 7	Usually 4	Always 3	No
Cost relative to net benefit	Very large 0	Large 1	Moderate 9	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

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